Using to Diagnose Cancer Using the Cancer Transcriptome

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Abstract

Targeting operable mutations in cancer driver genes has helped precision oncology make major strides. Recent research has started to look into the potential of tumor transcriptome to direct patient treatment in an effort to increase treatment options. Here, we offer SELECT (synthetic lethality and rescue-mediated precision oncology via the transcriptome), a framework for precision oncology that uses genetic interactions to forecast patient response to cancer therapy from the transcriptome of the tumour. 35 published targeted and immunotherapy clinical trials from 10 distinct cancer types are used as a large sample for the testing of SELECT. In 80% of these clinical trials and the most recent multi-arm WINTHER experiment, it accurately predicts the patients' responses. The code and predicted signatures are made available for academic usage in the public, providing a foundation for potential future clinical research

Keywords: Precision oncology • Synthetic lethality • Synthetic rescues • Transcriptomics • Cancer immunotherapy • Patient stratification antibody • Adoptive cell therapy • Precision medicine

Introduction

With the growing use of sequencing tests that pinpoint targetable mutations in cancer driver genes, precision oncology has made considerable strides. Recent research has begun to investigate the use of transcriptomics data to direct cancer patients' therapy, with the aim of completing these efforts by taking into account genome-wide tumour mutations at additional "-omics" levels. These research have shown promising findings, attesting to the potential of such strategies to supplement mutation panels and raise the probability that patients may benefit from genomics-guided precision medicine. The necessity for developing and evaluating new systematic methodologies is increased by the fact that present methods for using tumour transcriptomics data to direct patient treatments are still of a heuristicexploratory character. Here, we introduce SELECT (Synthetic Lethality And Rescue-Mediated Precision Oncology via the Transcriptome), a precision oncology framework for choosing the best treatments for a given patient based on the tumour transcriptome. Unlike recent transcriptome-based methods that emphasise matching drugs to their targets' expression Our method is based on the discovery and application of the broader range of Genetic Interactions (GIs) of drug targets, which offer biologically testablebiomarkers for therapy response prediction. We use two recently published computational pipelines that identify genetic dependencies that are supported by multiple layers of omics data, such as in vitro functional screens, patient tumour DNA and RNA-Sequencing (RNA-seq) data, and phylogenetic profile similarity across various species, to identify the SL and SR partners of cancer drugs. Using these pipelines, we have previously been successful in identifying a Gq-driver mutation as a marker for FAK inhibitor SL treatment in uveal melanoma and a synergistic SL combination for treating melanoma and pancreatic tumours with asparaginase and Mitogen-Activated Protein Kinase (MAPK) inhibitors. We also discovered SR interactions in melanoma that mediate resistance to checkpoint treatments. However, the fundamental question of whether genetic dependencies derived from multi-omics tumour data may be used to predict effective therapies for specific cancer patients has not yet been answered. Here, we offer and investigate a computational framework called SELECT to take on this problem. The outcome is a systematic method for accurately predicting patients' responses to targeted and immune therapies across a broad range of therapies and cancer types, providing an alternative method to supplement current mutation-based methods.

Discussion

We have shown that one may computationally derive potential pairings of GIs that can be utilised as predictive biomarkers for a variety of targeted and immunotherapy treatments, across many cancer types. This is done by mining large-scale "-omics" data from patient tumours. For several of the medicines examined, the resulting prediction accuracy is high. Furthermore, as revealed in the analysis of the WINTHER trial, its use offers a promising strategy to increase the number of patients who could profit from precision-based medicines, which should be further investigated in prospective trials. In two significant ways, SELECT is fundamentally distinct from earlier attempts to predict the therapy response. Pre-treatment data from the TCGA ensemble is analysed to determine the SL/SR interactions that underlie the prediction. These interactions are then further filtered using very little training on a single treatment response dataset to create a small number of classification hyper-parameters. The predictors produced by this method are anticipated to be less vulnerable to the risk of overfitting, which typically occurs when modern supervised predictors are built by training on the relatively small clinical datasets. The SL/SR interactions used in this study are also common across a wide range of cancer kinds, making them less context-sensitive and more likely to be predictive across a range of cancer types. As opposed to the typical "black-box" solutions typical of machine learning approaches, the functional interpretation of the emerging SL/SR interactions and their scoring are straightforward and intuitive. This makes it noteworthy that the interactions enabling the predictions have clear biological meanings. In comparison to current predictors, SELECT performs prediction better. In as many targeted and immunotherapy datasets as we are aware, no single model has ever been demonstrated to achieve such predictive accuracy. Conveniently, SELECT maintains its prediction accuracy when multiple cohorts are combined, despite the fact that many of the currently available immune checkpoint cohorts are small.