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PREDICTION OF DRUG EFFICACY FROM TRANSCRIPTIONAL PROFILES WITH DEEP LEARNING

Zhengwei Xie

Peking University Health Science Center, China

Drug discovery focused on target proteins has been a successful strategy, but many diseases and biological processes lack obvious targets to enable such approaches. Here, to overcome this challenge, we describe a deep learning–based efficacy prediction system (DLEPS) that identifies drug candidates using a change in the gene expression profile in the diseased state as input. DLEPS was trained using chemically induced changes in transcriptional profiles from the L1000 project. We found that the changes in transcriptional profiles for previously unexamined molecules were predicted with a Pearson correlation coefficient of 0.74. We examined three disorders and experimentally tested the top drug candidates in mouse disease models. Validation showed that perillen, chikusetsusaponin IV and trametinib confer disease-relevant impacts against obesity, hyperuricemia and nonalcoholic steatohepatitis, respectively. DLEPS can generate insights into pathogenic mechanisms, and we demonstrate that the MEK–ERK signaling pathway is a target for developing agents against nonalcoholic steatohepatitis. Our findings suggest that DLEPS is an effective tool for drug repurposing and discovery.