学 位 論 文 の 要 旨

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主論文の題名

An Integrated In Silico and In Vivo Approach to Identify Protective Effects of Palonosetron in Cisplatin-Induced Nephrotoxicity

主論文の要旨

Cisplatin is widely used to treat various types of cancers, but it is often limited by nephrotoxicity. We employed an integrated in silico and in vivo approach to identify potential treatments for cisplatin-induced nephrotoxicity (CIN). Using publicly available mouse kidney and human kidney organoid transcriptome datasets, we first identified a 208-gene expression signature for CIN and then used the bioinformatics database Cmap and Lincs Unified Environment (CLUE) to identify drugs expected to counter the expression signature for CIN. We also searched the adverse event database, Food and Drug Administration Adverse Event Reporting System (FAERS), to identify drugs that reduce the reporting odds ratio of developing cisplatin-induced acute kidney injury. Palonosetron, 5-hydroxytryptamine receptor 3 (5-HT3R) antagonist, was identified by both CLUE and FAERS analyses. Notably, clinical data from 103 patients treated with cisplatin for head and neck cancer revealed that palonosetron was superior to ramosetron in suppressing cisplatin-induced increases in serum creatinine and blood urea nitrogen levels. Moreover, palonosetron significantly increased the survival rate of zebrafish exposed to cisplatin but not to other 5-HT3R antagonists. These results not only suggest that palonosetron can suppress CIN but also support the use of in silico and in vivo approaches in drug repositioning studies.