IDENTIFICATION OF PROTEINS ASSOCIATED WITH DRUG-INDUCED LIVER INJURY USING *IN SILICO* PREDICTION OF DRUG-TARGET INTERACTIONS

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Motivation and Aim: Drug-induced liver injury (DILI) is the leading cause of acute liver failure as well as one of the major cases of drug withdrawn from clinical trials and the market. Understanding of DILI-related mechanisms may help to improve the existing and develop new methods of DILI detection on the earliest stages of drug development. Most of the investigations focused on the formation of toxic or reactive metabolites, whereas specific interactions with protein targets are accepted to be the primary cause of many other adverse drug effects [1, 2].
Methods and Algorithms: Specific DILI-related protein targets were identified through the analysis of drug-target interactions which were predicted by PASS Targets software [3]. It predicts interactions with 1534 human targets. The study was carried out using a dataset containing 178 severe DILI-causing drugs, 310 moderate DILI-causing drugs and 211 non-DILI-causing drugs, which was created based on mainly SIDER (http://sideeffects.embl.de/) and LiverTox (http://livertox.nih.gov/) databases.
Results: Statistical analysis of predicted drug-target interactions of dataset's compounds coupled with analysis of Gene Ontology allows revealing 145 protein targets putatively associated with DILI as well as cellular pathophysiological processes leading to DILI. Most of the revealed processes were associated with hepatocytes, the main from which was apoptosis. Interactions with proteins which were involved in immune system regulation were also identified. About half of DILI-causing drugs from various chemical-therapeutic classes interact with the revealed targets. We clustered drugs based on their interactions with 145 targets and confirmed correlations with DILI within clusters for 61 from those targets. These 61 protein targets are possibly the most essential for DILI development.
Conclusion: We found that interaction with the identified specific protein targets has a major role in the development of severe DILI.

References:
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