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Opinion Article

Evaluating the Sensitivity of HL-ICOs to Hepatotoxicants: Implications for *In Vitro* Toxicity Assessment

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DESCRIPTION

New developments in in vitro toxicity testing make an effort to address the demand for trustworthy human-based safety evaluation in medication development. The term "Intrahepatic Cholangiocyte Organoids" (ICOs) refers to an *in vitro* disease model for regenerative medicine that is developed from a donor. Here, we investigated the expression and activity of genes implicated in drug metabolism, a significant factor in drug-induced toxicity, and the exposure of Hepatocyte-like ICOs (HL-ICOs) to well-known hepatotoxicants in order to examine the potential of HL-ICOs in in vitro toxicity testing. In terms of CYP3A4 expression, HL-ICOs' drug metabolism was equivalent to that of Preventive Health and Health services (PHHs) and HepaRGs, while other enzymes, such CYP2B6 and CYP2D6, were expressed at lower levels. EC50 values for acetaminophen were also calculated in HL-ICOs (24.0–26.8 mM) Troglitazone (23.1-90.8 M), diclofenac (475.5–500 M), perhexiline (9.7–31.5 M), and valproic acid (>10 mM). When exposed to the hepatotoxicants, HL-ICOs had EC50s that were equivalent to those of PHHs and HepaRGs, although they were less susceptible to acetaminophen. For the purpose of correctly defining the potential of HL-ICOs in in vitro toxicity assessment, more understanding of enzyme and transporter activities in drug metabolism in HL-ICOs and exposure to a larger chemical collection are required.

One of the main factors affecting medication-induced toxicity is drug metabolism. The liver is vulnerable to damage brought on by drugs since it is essential for drug metabolism. Drug-Induced Liver Damage (DILI) continues to be a primary reason for stopping drug development and removing medications from the market, despite the adoption of cutting-edge human-based methodologies in drug development such as *in vitro* and *in silico* pre-clinical testing. To enhance toxicity prediction and further reduce adverse medication responses, it is crucial to get human-relevant mechanistic insights into DILI. Drug metabolism in the liver typically occurs in two steps. To enable phase II enzymes to conjugate the drug and speed up excretion, polar functional groups are added to or opened up during phase I. Phase I biotransformation enzymes belong to the cytochrome P450 (CYP) superfamily, which is the most well-known and extensively researched group. Bioactivation from CYP oxidation frequently results in DILI. Many human CYP isoforms, such as CYP2B6, CYP2C9, and CYP2D6, have genetic variations that are a common cause of bad medication responses necessitating hospitalisation.

In general, phase II metabolism is a detoxification process that balances the reactivity of intermediate metabolites by the action of Uridine 5'-Diphospho-glucuronosyltransferases (UDP-Glucuronosyltransferases, UGTs), Sulfotransferases (SULTs), and Glutathione Transferases (GSTs). Drugs and their conjugated metabolites are excreted *via* hepatic transporters, which include the superfamilies ATP-binding cassette (ABC) transporters and Solute Carrier (SLC) transporters. A further risk factor for drug-drug interactions and DILI is the inhibition of efflux transporters, which results in intracellular accumulation.

Due to their roles in the deactivation and excretion of substances, these two stages of drug metabolism and the performance of hepatic transporters are essential to understanding hepatotoxicity. Although pharmacokinetics in patients and hepatotoxic potency of novel medications are often predicted in animal models, there are significant interspecies and interindividual variations in the expression and function of drug metabolic enzymes and transporters. In order to gather data on human-based toxicity as well as to replace, decrease, and improve the use of animals in safety studies, non-animal alternatives have developed over time. Hepatic human *in vitro* models must exhibit morphological and functional characteristics, such as drug metabolism, similar to an *in vivo* condition in order to carry out trustworthy human-based toxicity screenings or mechanistic investigations into DILI pathways.

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