Transcriptomic mapping of the inter-individual variability of cellular stress response activation in primary human hepatocytes

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INTRODUCTION

Drug-induced liver injury (DILI) remains a major concern for the clinic and pharmaceutical companies, and therefore there is a need to improve its prediction at an early phase during drug development. One of the early key events of DILI is the activation of adaptive stress responses, a cellular mechanism to overcome stress. Given the diversity of DILI outcomes, it is key to map the inter-individual variability in activation of these stress responses. Accurately capturing this variance, could aid in the improvement of drug toxicity screening strategies.

METHODOLOGY

Therefore, in a high-throughput fashion we profiled the transcriptome of a panel of 50 cryo-preserved primary human hepatocytes derived from different individuals exposed for 8 or 24 h to a broad concentration range of tunicamycin for unfolded protein response (UPR), diethyl maleate for oxidative stress response, cisplatin for DNA damage response and TNF α for NF-κB signalling. Transcriptomic profiles were related to LDH leakage as a measure for cytotoxicity.

RESULTS

The variance in the concentration-dependent stress response activation among individuals could be captured, where the average of benchmark concentrations (BMCs) had a maximum difference of 864, 13, 13 and 259-fold between different hepatocytes for UPR, oxidative stress, DNA damage and NF-κB signalling-related genes, respectively. Hepatocytes from patients with liver disease resulted in less stress response activation. Given that often a small panel of PHHs is used during drug toxicity screening, the influence of the panel size on the estimation of the variance in stress response activation was evaluated. Using a population mixed-effect framework, the distribution of the BMCs and maximum fold change were modelled, allowing simulation of smaller or larger PHH panel sizes. Small panel sizes

systematically under-estimated the variance and resulted in low probabilities in estimating the correct variance for the human population. Moreover, estimated toxicodynamic variability factors were up to 2-fold higher than the standard uncertainty factor of 101/2 to account for population variability during risk assessment, exemplifying the need of data-driven variability factors.

DISCUSSION

Overall, by combining high-throughput transcriptome analysis and population modelling, improved understanding of variability in stress response activation across the human population could be established, thereby contributing towards improved prediction of DILI.

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