Use of a non-hepatic cell line highlights limitations associated with cell-based assessment of metabolically induced toxicity

Carli Weyers, Laura M. K. Dingle, Brendan S. Wilhelmi, **Adrienne L. Edkins** & **Clinton G. L. Veale**

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Abstract

Metabolically induced drug-toxicity is a major cause of drug failure late in drug optimization phases. Accordingly, *in vitro* metabolic profiling of compounds is being introduced at earlier stages of the drug discovery pipeline. An increasingly common method to obtain these profiles is through overexpression of key CYP450 metabolic enzymes in immortalized liver cells, to generate competent hepatocyte surrogates. Enhanced cytotoxicity is presumed to be due to toxic metabolite production via the overexpressed enzyme. However, metabolically induced toxicity is a complex multi-parameter phenomenon and the potential background contribution to metabolism arising from the use of liver cells which endogenously express CYP450 isoforms is consistently overlooked. In this study, we sought to reduce the potential background interference by applying this methodology in kidney-derived HEK293 cells which lack endogenous CYP450 expression. Overexpression of CYP3A4 resulted in increased HEK293 proliferation, while exposure to four compounds with reported metabolically induced cytotoxicity in liver-derived cells overexpressing CYP3A4 resulted in no increase in cytotoxicity. Our results indicate that overexpression of a single CYP450 isoform in hepatic cell lines may not be a reliable method to discriminate which enzymes are responsible for metabolic induced cytotoxicity.