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Human hepatic HepaRG cells maintain high intrinsic CYP450 activity/metabolism and significantly outperform standard HepG2/C3A cells used in drug pharmacology applications

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BACKGROUND

- Conventional in vitro human hepatic models for drug testing are based on the use of standard cell lines or primary human hepatocytes (PH-Hep).
- However, limited availability, inter-donor functional variability and early phenotypic alterations of PH-Hep in vitro restrict their use, while cell lines such as HepG2/C3A lack a substantial and variable set of liver-specific functions, apically, CYP450 activity.
- Human HepaRG cells are an alternative orthotypic co-culture model of hepatocytes and cholangiocytes that maintains in vivo-like liver-specific functions, including intact Phase-I and drug and lipid metabolism.

METHODS

- HepG2/C3A or HepaRG were grown to >90% confluence on collagen-I coated plates and treated (in triplicates) for 24 h with prototypical inducers rifampicin (CYP3A4) and omeprazole (CYP1A2) [1-3].

RESULTS

- HepaRG [left panel] and HepG2/C3A [right panel] showed markedly different abundance of CYP3A4, as indicated by immunofluorescent staining against a marker panel consisting of CYP3A4, hepatoid or DAPI staining.

CONCLUSIONS

- Only HepaRG cells retain differentiated morphological/phenotypic features relevant to drug testing strategies.
- Analytical techniques including LC-MS/MS allow HepaRG cells to be interrogated for drug reactive metabolite formation — allowing intrinsic (predictive) drug clearance rates to be calculated.
- HepaRG cells may represent a more physiologically-relevant pre-clinical platform for CYP450 activation/inhibition, safety pharmacology, as well as drug-drug interaction studies.