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Editorial:

HEPATOTOXICITY

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Research on hepatotoxicity has been intensified in recent years. This can be partly explained by large projects such as the German project Virtual Liver with more than 60 partners and the EU project NoTox where hepatocyte in vitro systems are applied and optimized. Hepatocyte cultures are well accepted in vitro systems in both pharmacology and toxicology (Hengstler et al., 2009a, b; Gebhardt et al., 2003; Hewitt et al., 2007; Godoy et al., 2010a, b; Meyer et al., 2011). However, following isolation from the liver and attachment to the matrix of a culture dish, primary hepatocytes undergo major alterations, often referred to as dedifferentiation (Godoy et al., 2009; Zellmer et al., 2010). In contradiction to previous concepts, hepatocyte dedifferentiation is not a passive process during which some function are lost but represents an active response of the hepatocytes to the novel environment. This involves focal adhesion kinase mediated activation of PI3k/Akt and Raf/Mek/Erk signalling. Further progress in the field of hepatotoxicity will depend on whether it will become possible to optimize culture conditions, so that cultivated hepatocytes better reflect the in vivo situation. It is therefore understandable that several of the recent publications have used hepatocytes in vitro, either to opitimize techniques, such as hypothermic preservation (Ostrowska et al., 2009) or to understand mechanisms of toxicity (e.g., Nakagawa et al., 2009; Arafa, 2009). A second cutting-edge topic is alcohol induced fatty liver which is addressed in two comprehensive articles (Zeng and Xie, 2009; Cederbaum et al., 2009) giving an overview over the key mechanisms, namely changes of the redox condition, transportation of lipids, altered fatty acid oxidation and the enhancement of lipogenesis.

Table 1: Recent studies on hepatotoxicity

Key message	Reference
Benzylpenicillin (BPCN) is an efficient antidote against amanitins in human hepatocytes.	Magdalan et al., 2009
Toxotrienol caused nodular hepatocellular hyperplasia (NHH) in a 104-week carcinogenicity study in rats. However NHH did not become neoplastic.	Tasaki et al., 2009
Alcohol induced fatty liver is a frequent health problem without effective therapy. This review addresses relevant mechanisms, including changes of the redox condition, transportation impairment of lipids, compromised fatty acid oxidation and the enhancement of lipogenesis with a focus on PPAR α and SREBP-1.	Zeng and Xie, 2009
Adequate animal models to predict idiosyncratic drug induced liver injury (DILI) represent a cutting-edge topic in toxicology. This study shows that aodiaquine induces hepatotoxicity in mice only after depletion of glutathione.	Shimizu et al., 2009

Table 1 (cont.): Recent studies on hepatotoxicity

Key message	Reference
The perfluorinated compounds PFOA and PFOS are widely distributed in the environment. The current study addresses possible interactions between both compounds in a human hepatoma cell line. However, only a summation effect was observed.	Hu and Hu, 2009
Trichloroethylene is known to cause hepatocellular cancer in mice. Microarray analysis after oral administration of trichloroethylene revealed inhibition of the TGF-beta and activation of the MAPK signalling pathways.	Sano et al., 2009
This review focusses on key mechanisms of alcohol-induced liver injury: production of reactive oxygen species, depletion of antioxidants and induction of CYP2E1.	Cederbaum et al., 2009; Hengstler et al., 2009a (editorial)
To study which of several hypothermic preservation media lead to optimal results, primary human hepatocytes were analyzed after storage at 4 °C for 24-72 h. The best results were obtained with HypoThermosol-FRS.	Ostrowska et al., 2009
A novel rapid and easy to handle thermoluminescence assay has been established to quantify oxidative stress in primary hepatocytes.	Schumann et al., 2009
This study presents the toxicokinetics of arsenic species in the liver of mice.	Juárez-Reyes et al., 2009
This short editorial summarizes some current technical limitations of hepatocyte in vitro systems.	Hengstler et al., 2009b
Alpha-tocopherol ameliorates CCL_4 induced liver necrosis and restores hepatic vitamin C concentration.	Iida et al., 2009
Tert-butyl hydroperoxide drecreases intracellular glutathione and mitochondrial membrane potential in rat hepatocytes.	Cervinková et al., 2009
Alpha-amanitin shows a biphasic course of toxicity in cultivated dog hepatocytes with inhibition of protein and urea synthesis, marginalization and condensation of nuclear chromatin in a first phase, and necrosis and apoptosis in a second phase.	Magdalan et al., 2009
Using a rat hepatocarcinogenesis model the anthelmintic oxfendazole shows tumor promoting activity by generation of reactive oxygen species.	Dewa et al., 2009
Quinacrine inhibits CYP2E1 in rat livers and protects against genotoxicity by the CYP2E1 activated tobacco specific nitrosamine NNK.	Karamanakos et al., 2009
4-Tert-octylphenol causes liver toxicity in rats.	Barlas and Aydoğan, 2009
Carnitine deficiency increases susceptibility to paracetamol induced hepatotoxicity.	Arafa, 2009
The amphetamine-derived designer drugs MDMA and MBDB induce mitochondrial depolarization and cause DNA damage in rat hepatocytes.	Nakagawa et al., 2009

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