Arch Toxicol (2017) 91:2963–2964
DOI 10.1007/s00204-017-2019-5

GUEST EDITORIAL

Highlight report: co-cultures of hepatocytes and macrophages for hepatotoxicity testing

Abdel-latif Seddek[1] · **Aya A. Abbas**[1]

Received: 12 June 2017 / Accepted: 20 June 2017 / Published online: 29 June 2017

Recently, Wewering et al. (2017) from the Department of Chemical and Product Safety in Berlin have published a study about a co-culture system that aims to simulate hepatocyte–macrophage interactions. It is well established that complex interactions between hepatocytes and non-parenchymal cells take place during induction of liver toxicity (Baeck and Tacke 2014; Hammad et al. 2014; Hoehme et al. 2010). Particularly, neutrophilic granulocytes and macrophages have been reported to aggravate the damage induced by hepatotoxic compounds (Adams et al. 2010; Jaeschke et al. 2012; Marques et al. 2012, 2015; Dong et al. 2007). Nevertheless, current in vitro testing for hepatotoxicity mostly relies on hepatocyte cultures without addition of immune cells (Grinberg et al. 2014; Valente et al. 2016; Arbo et al. 2016; Deharde et al. 2016; Ghallab et al. 2016; Ramboer et al. 2015; Godoy et al. 2016; Hammad et al. 2015). Currently, it remains unclear whether co-cultures of hepatocytes with immune cells really improve hepatotoxicity testing. One challenge studying this task is to avoid spontaneous activation of immune cells in vitro. To gain more insight into hepatocyte–immune cell interactions, Wewering et al. (2017) compared cultures of HepG2 cells alone to co-cultures of HepG2 cells and the macrophage cell line THP-1.

Interestingly, the hepatotoxic compound ketoconazole induced secretion of the pro-inflammatory cytokines CXCL8, TNF-α and CCL3 only in the co-culture system but not in HepG2 mono-cultures. The study presents clear evidence that co-cultures of immune cells and hepatocytes may indeed improve in vitro hepatotoxicity testing. Limitations of the current study are that so far only one compound has been tested and that no primary cells could be used. Nevertheless, the study of Wewering et al. is of high interest and further studies are needed to gain deeper insight as to which degree hepatocyte–immune cell interactions can be simulated in vitro.

✉ Abdel-latif Seddek
abdellatief-shakir@vet.svu.edu.eg

[1] Forensic Medicine and Toxicology Department, Faculty of Veterinary Medicine, South Valley University, Qena, Egypt

References

Adams DH, Ju C, Ramaiah SK et al (2010) Mechanisms of immune-mediated liver injury. Toxicol Sci 115:307–321

Arbo MD, Melega S, Stöber R, Schug M, Rempel E, Rahnenführer J, Godoy P, Reif R, Cadenas C, de Lourdes Bastos M, Carmo H, Hengstler JG (2016) Hepatotoxicity of piperazine designer drugs: up-regulation of key enzymes of cholesterol and lipid biosynthesis. Arch Toxicol 90(12):3045–3060 **(Epub 2016 Jan 28)**

Baeck C, Tacke F (2014) Balance of inflammatory pathways and interplay of immune cells in the liver during homeostasis and injury. Excli J 13:67–81

Deharde D, Schneider C, Hiller T, Fischer N, Kegel V, Lübberstedt M, Freyer N, Hengstler JG, Andersson TB, Seehofer D, Pratschke J, Zeilinger K, Damm G (2016) Bile canaliculi formation and biliary transport in 3D sandwich-cultured hepatocytes in dependence of the extracellular matrix composition. Arch Toxicol 90(10):2497–2511. doi:10.1007/s00204-016-1758-z **(Epub 2016 Jun 21)**

Dong Z, Wei H, Sun R, Tian Z (2007) The roles of innate immune cells in liver injury and regeneration. Cell Mol Immunol 4:241–252

Ghallab A, Cellière G, Henkel SG, Driesch D, Hoehme S, Hofmann U, Zellmer S, Godoy P, Sachinidis A, Blaszkewicz M, Reif R, Drasdo D, Gebhardt R, Hengstler JG (2016) Model-guided identification of a therapeutic strategy to reduce hyperammonemia in liver diseases. J Hepatol 64(4):860–871. doi:10.1016/j.jhep.2015.11.018

Godoy P, Widera A, Schmidt-Heck W et al (2016) Gene network activity in cultivated primary hepatocytes is highly similar to diseased mammalian liver tissue. Arch Toxicol 90(10):2513–2529. doi:10.1007/s00204-016-1761-4 **(Epub 2016 Jun 23)**

Grinberg M, Stöber RM, Edlund K et al (2014) Toxicogenomics directory of chemically exposed human hepatocytes. Arch Toxicol 88(12):2261–2287. doi:10.1007/s00204-014-1400-x **(Epub 2014 Nov 16)**

Hammad S, Hoehme S, Friebel A et al (2014) Protocols for staining of bile canalicular and sinusoidal networks of human, mouse and pig livers, three-dimensional reconstruction and quantification of tissue microarchitecture by image processing and analysis. Arch Toxicol 88(5):1161–1183. doi:10.1007/s00204-014-1243-5

Hammad S, Abdel-Wareth A, El-Sayed YS (2015) In vitro-in vivo correlation: hepatotoxicity testings. JEASS 1(3):384–387

Hoehme S, Brulport M, Bauer A, Bedawy E, Schormann W, Hermes M, Puppe V, Gebhardt R, Zellmer S, Schwarz M, Bockamp E, Timmel T, Hengstler JG, Drasdo D (2010) Prediction and validation of cell alignment along microvessels as order principle to restore tissue architecture in liver regeneration. Proc Natl Acad Sci USA 107(23):10371–10376

Jaeschke H, Williams CD, Ramachandran A, Bajt ML (2012) Acetaminophen hepatotoxicity and repair: the role of sterile inflammation and innate immunity. Liver Int 32:8–20

Marques PE, Amaral SS, Pires DA et al (2012) Chemokines and mitochondrial products activate neutrophils to amplify organ injury during mouse acute liver failure. Hepatology 56:1971–1982

Marques PE, Oliveira AG, Pereira RV et al (2015) Hepatic DNA deposition drives drug-induced liver injury and inflammation in mice. Hepatology 61:348–360

Ramboer E, Rogiers V, Vanhaecke T, Vinken M (2015) Effects of trichostatin A on drug uptake transporters in primary rat hepatocyte cultures. Excli J 14:567–576

Valente MJ, Araújo AM, Silva R, Bastos Mde L, Carvalho F, Guedes De Pinho P, Carvalho M (2016) 3,4-Methylenedioxypyrovalerone (MDPV): in vitro mechanisms of hepatotoxicity under normothermic and hyperthermic conditions. Arch Toxicol 90(8):1959–1973. doi:10.1007/s00204-015-1653-z **(Epub 2015 Dec 16)**

Wewering F, Jouy F, Wissenbach DK, Gebauer S, Blüher M, Gebhardt R, Pirow R, von Bergen M, Kalkhof S, Luch A, Zellmer S (2017) Characterization of chemical-induced sterile inflammation in vitro: application of the model compound ketoconazole in a human hepatic co-culture system. Arch Toxicol 91(2):799–810. doi:10.1007/s00204-016-1686-y **(Epub 2016 Mar 10)**