

Guest editorial:

**INTEGRATED SPATIOTEMPORAL-METABOLIC MODELLING
BRIDGES THE GAP BETWEEN METABOLISM ON THE
CELLULAR LEVEL AND ORGAN FUNCTION**

Agata Widera

Leibniz Institut für Arbeitsforschung an der TU Dortmund,
Leibniz Research Centre for Working Environment and Human Factors (IfADo),
Ardeystrasse 67, 44139 Dortmund, Germany; widera@ifado.de

Recently, Schliess et al. (2014) have introduced a novel concept of spatiotemporal modelling. This work is of general interest, because it offers a possibility to bridge the level of metabolic functions at the subcellular level to tissue architecture and organ function. The authors used an already established spatiotemporal model of a liver lobule (Hoehme et al., 2010; 2007). This model simulates the position and coordinated movement of all hepatocytes in a representative lobule during the destruction and regeneration process after intoxication with hepatotoxic compounds. Moreover, it contains the microvessel of the liver lobule that allows simulation of perfusion and drug transport. The authors used this model to additionally integrate metabolic process into the simulated hepatocytes (Schliess et al., 2014). Metabolic pathways of ammonia metabolism, the urea cycle in periportal and glutamine synthetase in the pericentral compartment of the liver lobule, were modelled as differential equations and integrated into the hepatocytes of the spatiotemporal model. The resulting integrated model allows the simulation of ammonia and its metabolites in the liver vein (the ‘liver outflow’) for a given concentration in the portal vein (the ‘liver inflow’). Moreover, the model predicts to which degree a certain extent or pattern of liver tissue destruction will compromise ammonia detoxification. This novel technique of integrated spatiotemporal tissue modelling may have a major impact on stud-

ies of organ toxicity in future (Wierling, 2014; Godoy et al., 2013; Drasdo et al., 2014; Hammad et al., 2014). Currently, studies on hepatotoxicity are often performed *in vivo* in rodents (Nussler et al., 2014; Zhang et al., 2013; Ghallab, 2013; Kanda et al., 2008; Monteiro et al., 2013; Köhle et al., 2008; Jaeschke et al., 2012; van Kesteren et al., 2013; Hammad et al., 2013; Hadi et al., 2013; Lo et al., 2012). On the other hand *in vitro* systems with hepatocytes represent a popular system to analyse molecular mechanisms (Messner et al., 2013; Godoy et al., 2009, 2010a, b; Hengstler et al., 2009; Klingmüller et al., 2006; Schyschka et al., 2013; Watzek et al., 2013; Muguruma et al., 2008; Grinberg et al., 2014; Schaap et al., 2012; Schug et al., 2013; Doktorova et al., 2012a, b; Ilkavets, 2013; Gagné et al., 2012; Fraczek et al., 2013; Fernandes et al., 2003). Although cultivated hepatocytes represent a valuable tool to qualitatively study molecular mechanisms it still is difficult to extrapolate their impact at the organ level. The work of Schliess et al. (2014) is a first step in establishing modelling techniques that bridge the levels of intra or even subcellular metabolic pathways to the functionality and metabolic performance of entire organs.

REFERENCES

- Doktorova TY, Ellinger-Ziegelbauer H, Vinken M, Vanhaecke T, van Delft J, Kleinjans J, et al. Comparison of genotoxicant-modified transcriptomic responses in conventional and epigenetically stabilized primary rat hepatocytes with *in vivo* rat liver data. Arch Toxicol. 2012a;86:1703-15.
- Doktorova TY, Ellinger-Ziegelbauer H, Vinken M, Vanhaecke T, van Delft J, Kleinjans J, et al. Comparison of hepatocarcinogen-induced gene expression profiles in conventional primary rat hepatocytes with *in vivo* rat liver. Arch Toxicol. 2012b;86:1399-411.
- Drasdo D, Hoehme S, Hengstler JG. How predictive quantitative modelling of tissue organisation can inform liver disease pathogenesis. J Hepatol. 2014;61:951-6.
- Fernandes E, Carvalho M, Carvalho F, Silva AM, Santos CM, Pinto DC, et al. Hepatoprotective activity of polyhydroxylated 2-styrylchromones against tert-butylhydroperoxide induced toxicity in freshly isolated rat hepatocytes. Arch Toxicol. 2003;77:500-5.
- Fraczek J, Bolleyn J, Vanhaecke T, Rogiers V, Vinken M. Primary hepatocyte cultures for pharmacotoxicological studies: at the busy crossroad of various anti-dedifferentiation strategies. Arch Toxicol. 2013;87:577-610.
- Gagné F, André C, Skirrow R, Gélinas M, Auclair J, van Aggelen G, et al. Toxicity of silver nanoparticles to rainbow trout: a toxicogenomic approach. Chemosphere. 2012;89:615-22.
- Ghallab A. *In vitro* test systems and their limitations. EXCLI J 2013;12:1024-6.
- Godoy P, Hengstler JG, Ilkavets I, Meyer C, Bachmann A, Müller A, et al. Extracellular matrix modulates sensitivity of hepatocytes to fibroblastoid dedifferentiation and transforming growth factor beta-induced apoptosis. Hepatology. 2009;49:2031-43.
- Godoy P, Schug M, Bauer A, Hengstler JG. Reversible manipulation of apoptosis sensitivity in cultured hepatocytes by matrix-mediated manipulation of signaling activities. Methods Mol Biol. 2010a;640:139-55.
- Godoy P, Lakkapamu S, Schug M, Bauer A, Stewart JD, Bedawi E, et al. Dexamethasone-dependent versus -independent markers of epithelial to mesenchymal transition in primary hepatocytes. Biol Chem. 2010b;391:73-83.
- Godoy P, Hewitt NJ, Albrecht U, Andersen ME, Ansari N, Bhattacharya S, et al. Recent advances in 2D and 3D *in vitro* systems using primary hepatocytes, alternative hepatocyte sources and non-parenchymal liver cells and their use in investigating mechanisms of hepatotoxicity, cell signaling and ADME. Arch Toxicol. 2013;87:1315-530.
- Grinberg M, Stöber RM, Edlund K, Rempel E, Godoy P, Reif R, et al. Toxicogenomics directory of chemically exposed human hepatocytes. Arch Toxicol. 2014;88:2261-87.
- Hadi M, Dragovic S, van Swelm R, Herpers B, van de Water B, Russel FG, et al. AMAP, the alleged non-toxic isomer of acetaminophen, is toxic in rat and human liver. Arch Toxicol. 2013;87:155-65.
- Hammad S, Marchan R, Hengstler JG. Cutting-edge topics in research on animal sciences. J Exp Appl Animal Sci. 2013;1(1):1-3.
- Hammad S, Hoehme S, Friebel A, von Recklinghausen I, Othman A, Begher-Tibbe B, et al. 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. 2014;88:1161-83.
- Hengstler JG, Godoy P, Bolt HM. The dilemma of cultivated hepatocytes. Arch Toxicol. 2009;83:101-3.
- Hoehme S, Hengstler JG, Brulport M, Schäfer M, Bauer A, Gebhardt R et al. Mathematical modelling of liver regeneration after intoxication with CCl(4). Chem Biol Interact. 2007;168:74-93.
- Hoehme S, Brulport M, Bauer A, Bedawy E, Schormann W, Hermes M, et al. Prediction and validation of cell alignment along microvessels as order principle to restore tissue architecture in liver regeneration. Proc Natl Acad Sci USA. 2010;107:10371-6.
- Ilkavets I. A special issue about hepatotoxicity and hepatocyte *in vitro* systems. Arch Toxicol 2013;87:1313-4.
- Jaeschke H, Williams CD, McGill MR. Caveats of using acetaminophen hepatotoxicity models for natural product testing. Toxicol Lett. 2012;215:40-1.
- Kanda H, Sumi D, Endo A, Toyama T, Chen CL, Kikushima M, et al. Reduction of arginase I activity and manganese levels in the liver during exposure of rats to methylmercury: a possible mechanism. Arch Toxicol. 2008;82:803-8.
-

- Klingmüller U, Bauer A, Bohl S, Nickel PJ, Breitkopf K, Dooley S, et al. Primary mouse hepatocytes for systems biology approaches: a standardized *in vitro* system for modelling of signal transduction pathways. *Syst Biol (Stevenage)*. 2006;153:433-47.
- Köhle C, Schwarz M, Bock KW. Promotion of hepatocarcinogenesis in humans and animal models. *Arch Toxicol*. 2008;82:623-31.
- Lo WS, Lim YP, Chen CC, Hsu CC, Souček P, Yun CH, et al. A dual function of the furanocoumarin cholestin in inhibiting Cyp2a and inducing Cyp2b in mice: the protein stabilization and receptor-mediated activation. *Arch Toxicol*. 2012;86:1927-38.
- Messner S, Agarkova I, Moritz W, Kelm JM. Multi-cell type human liver microtissues for hepatotoxicity testing. *Arch Toxicol*. 2013;87:209-13.
- Monteiro JP, Pereira CV, Silva AM, Maciel E, Baldeiras I, Peixoto F, et al. Rapeseed oil-rich diet alters hepatic mitochondrial membrane lipid composition and disrupts bioenergetics. *Arch Toxicol*. 2013;87:2151-63.
- Muguruma M, Arai K, Moto M, Nishimura J, Dewa Y, Mitsumori K. Piperonyl butoxide activates c-Jun and ATF-2 in the hepatocytes of mice. *Arch Toxicol*. 2008;82:749-53.
- Nussler AK, Wildemann B, Freude T, Litzka C, Soldo P, Friess H, et al. Chronic CCl4 intoxication causes liver and bone damage similar to the human pathology of hepatic osteodystrophy: a mouse model to analyse the liver-bone axis. *Arch Toxicol*. 2014;88:997-1006.
- Schaap MM, Zwart EP, Wackers PF, Huijskens I, van de Water B, Breit TM, et al. Dissecting modes of action of non-genotoxic carcinogens in primary mouse hepatocytes. *Arch Toxicol*. 2012;86:1717-27.
- Schliess F, Hoehme S, Henkel SG, Ghallab A, Driesch D, Böttger J, et al. Integrated metabolic spatial-temporal model for the prediction of ammonia detoxification during liver damage and regeneration. *Hepatology*. 2014;60:2040-51.
- Schug M, Stöber R, Heise T, Mielke H, Gundert-Remy U, Godoy P, et al. Pharmacokinetics explain *in vivo/in vitro* discrepancies of carcinogen-induced gene expression alterations in rat liver and cultivated hepatocytes. *Arch Toxicol*. 2013;87:337-45.
- Schyschka L, Sánchez JJ, Wang Z, Burkhardt B, Müller-Vieira U, Zeilinger K, et al. Hepatic 3D cultures but not 2D cultures preserve specific transporter activity for acetaminophen-induced hepatotoxicity. *Arch Toxicol*. 2013;87:1581-93.
- van Kesteren PC, Zwart PE, Schaap MM, Pronk TE, van Herwijnen MH, Kleinjans JC, et al. Benzo[a]pyrene-induced transcriptomic responses in primary hepatocytes and *in vivo* liver: toxicokinetics is essential for *in vivo-in vitro* comparisons. *Arch Toxicol*. 2013;87:505-15.
- Watzek N, Scherbl D, Schug M, Hengstler JG, Baum M, Habermeyer M, et al. Toxicokinetics of acrylamide in primary rat hepatocytes: coupling to glutathione is faster than conversion to glycidamide. *Arch Toxicol*. 2013;87:1545-56.
- Wierling C. Bridging the gap between metabolic liver processes and functional tissue structure by integrated spatiotemporal modeling applied to hepatic ammonia detoxification. *Hepatology*. 2014;60:1823-5.
- Zhang Z, Sun ZZ, Xiao X, Zhou S, Wang XC, Gu J, et al. Mechanism of BDE209-induced impaired glucose homeostasis based on gene microarray analysis of adult rat liver. *Arch Toxicol*. 2013;87:1557-67.