

Guest editorial:

**BIOMARKER:
THE UNIVERSE OF CHEMICALLY INDUCED GENE EXPRESSION
ALTERATIONS IN HUMAN HEPATOCYTE**

Seddik Hammad^{1*}, Hassan Ahmed²

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

² Division of Cerebral Circuitry, National Institute for Physiological Sciences, Okazaki, Japan

*corresponding author e-mail: Seddik.hammad@vet.svu.edu.eg

In a recently published article Grinberg et al. (2014) analysed gene expression alterations induced by 148 compounds in cultivated human hepatocytes. The high number of analyzed compounds allowed a comprehensive study of the key features of chemically up or downregulated genes. The authors revealed four key features that are of high interest for further studies in this field of toxicogenomics. First, a stereotypical stress response has been observed. When hepatocytes are exposed at close to cytotoxic concentrations, they respond with a very similar pattern of deregulated genes for different compounds. This stereotypical response can be differentiated from more specific gene expressions alterations that are induced only by individual or small numbers of compounds. Second, approximately 20 % of the chemically altered genes overlap with genes whose expression is deregulated in human liver disease, such as steatosis or fibrosis. Third, the numbers of biological functions of the chemically altered genes are limited. Although more than 2000 genes are up or downregulated they mostly can be assigned to the categories xenobiotic, energy and lipid metabolism, inflammation and immune response, protein modification, cytoskeletal organisation, stress response and DNA repair. Finally Grinberg et al. (2014) describe a set of ‘unstable baseline genes’, whose expression is already altered by the hepatocyte isolation

and cultivation process. Therefore, these genes should be interpreted with caution.

Currently, identification of biomarkers of toxicity is an intensively studied field of research (Kolisetty et al., 2013; Song et al., 2013; Black and Read, 2013; Pavanello and Lotti, 2012; Kim et al., 2012; Park et al., 2011; Delaney et al., 2005; Angerer et al., 1998; Usuda et al., 1998). Within this field, gene expression analyses are particularly popular, because of the possibility of genome-wide analyses (Van Kesteren et al., 2013; Jennings et al., 2012; Drasdo et al., 2014; Hrach et al., 2011; Guo et al., 2008; Page et al., 2007; Hammad et al., 2013). For example, identification of compounds inducing developmental neurotoxicity has been made possible based on gene expression analysis of differentiating stem cells (Weng et al., 2014; Zimmer et al., 2014; Waldmann et al. 2014; Leist et al., 2013; Krug et al., 2013; Powers et al., 2013; Bolt, 2013).

Much research has been invested into the development and optimization of in vitro systems (Frey et al., 2014; Theocharis et al., 1994; Godoy and Bolt, 2012; Schug et al., 2013; Godoy et al., 2009). Toxicogenomics will be particularly helpful to further develop these systems and define to which degree they correctly predict expression responses in vivo.

Although a high number of studies have been published in the field of toxicogenomics, they usually only comprise a relatively small number of compounds. The study of Grinberg et al. (2014) is the first that includes genome-wide expression data of more than 100 compounds and therefore is able to derive general principles how the universe of chemically altered gene is organized. The study together with the supplemental toxicotranscriptomics directory offers a valuable source for an optimal choice of candidate genes for biomarker evaluation studies.

REFERENCES

- Angerer J, Schildbach M, Krämer A. S-p-toluymercapturic acid in the urine of workers exposed to toluene: a new biomarker for toluene exposure. *Arch Toxicol.* 1998;72:119-23.
- Black RM, Read RW. Biological markers of exposure to organophosphorus nerve agents. *Arch Toxicol.* 2013;87:421-37.
- Bolt HM. Developmental neurotoxicity testing with human embryonic stem cell-derived in vitro systems: the novel FP7 ESNATS tests are available. *Arch Toxicol.* 2013;87:5-6.
- Delaney J, Hodson MP, Thakkar H, Connor SC, Sweatman BC, Kenny SP, et al. Tryptophan-NAD⁺ pathway metabolites as putative biomarkers and predictors of peroxisome proliferation. *Arch Toxicol.* 2005;79:208-23.
- Drasdo D, Bode J, Dahmen U, Dirsch O, Dooley S, Gebhardt R, et al. The virtual liver: state of the art and future perspectives. *Arch Toxicol.* 2014;88:2071-5.
- Frey O, Misun PM, Fluri DA, Hengstler JG, Hierlemann A. Reconfigurable microfluidic hanging drop network for multi-tissue interaction and analysis. *Nat Commun.* 2014;5:4250.
- Godoy P, Bolt HM. Toxicogenomic-based approaches predicting liver toxicity in vitro. *Arch Toxicol.* 2012;86:1163-4. doi: 10.1007/s00204-012-0892-5.
- 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.
- 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.
- Guo M, Gong L, He L, Lehman-McKeeman L, Wan YJ. Hepatocyte RXRalpha deficiency in matured and aged mice: impact on the expression of cancer-related hepatic genes in a gender-specific manner. *BMC Genomics.* 2008;28:9:403.
- Hammad S, Marchan R, Hengstler JG. Cutting-edge topics in research on animal sciences. *J Exp Appl Animal Sci.* 2013;1(1):1-3.
- Hrach J, Mueller SO, Hewitt P. Development of an in vitro liver toxicity prediction model based on longer term primary rat hepatocyte culture. *Toxicol Lett.* 2011;206:189-96.
- Jennings P, Weiland C, Limonciel A, Bloch KM, Radford R, Aschauer L, et al. Transcriptomic alterations induced by Ochratoxin A in rat and human renal proximal tubular in vitro models and comparison to a rat in vivo model. *Arch Toxicol.* 2012;86:571-89.
- Kim TH, Ahn MY, Lim HJ, Lee YJ, Shin YJ, De U, et al. Evaluation of metabolomic profiling against renal toxicity in Sprague-Dawley rats treated with melamine and cyanuric acid. *Arch Toxicol.* 2012;86:1885-97.
- Kolisetty N, Delker DA, Muralidhara S, Bull RJ, Cotruvo JA, Fisher JW, et al. Changes in mRNA and protein expression in the renal cortex of male and female F344 rats treated with bromate. *Arch Toxicol.* 2013;87:1911-25.
- Krug AK, Kolde R, Gaspar JA, Rempel E, Balmer NV, Meganathan K, et al. Human embryonic stem cell-derived test systems for developmental neurotoxicity: a transcriptomics approach. *Arch Toxicol.* 2013;87:123-43.
- Leist M, Ringwald A, Kolde R, Bremer S, van Thriel C, Krause KH, et al. Test systems of developmental toxicity: state-of-the art and future perspectives. *Arch Toxicol.* 2013;87:2037-42.
- Page JL, Johnson MC, Olsavsky KM, Strom SC, Zarbl H, Omiecinski CJ. Gene expression profiling of extracellular matrix as an effector of human hepatocyte phenotype in primary cell culture. *Toxicol Sci.* 2007;97:384-97.
- Park HJ, Oh JH, Park SM, Cho JW, Yum YN, Park SN, et al. Identification of biomarkers of chemically induced hepatocarcinogenesis in rasH2 mice by toxicogenomic analysis. *Arch Toxicol.* 2011;85:1627-40.

- Pavanello S, Lotti M. Biological monitoring of carcinogens: current status and perspectives. *Arch Toxicol.* 2012;86:535-41.
- Powers CM, Bale AS, Kraft AD, Makris SL, Trecki J, Cowden J, et al. Developmental neurotoxicity of engineered nanomaterials: identifying research needs to support human health risk assessment. *Toxicol Sci.* 2013;134:225-42.
- 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. doi: 10.1007/s00204-012-0999-8.
- Song M, Song MK, Choi HS, Ryu JC. Monitoring of deiodinase deficiency based on transcriptomic responses in SH-SY5Y cells. *Arch Toxicol.* 2013;87:1103-13.
- Theocharis SE, Souliotis VL, Panayiotidis PG. Suppression of interleukin-1 beta and tumour necrosis factor-alpha biosynthesis by cadmium in in vitro activated human peripheral blood mononuclear cells. *Arch Toxicol.* 1994;69:132-6.
- Usuda K, Kono K, Dote T, Nishiura K, Miyata K, Nishiura H, et al. Urinary biomarkers monitoring for experimental fluoride nephrotoxicity. *Arch Toxicol.* 1998;72:104-9.
- 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.
- Waldmann T, Rempel E, Balmer NV, König A, Kolde R, Gaspar JA, et al. Design principles of concentration-dependent transcriptome deviations in drug-exposed differentiating stem cells. *Chem Res Toxicol.* 2014;17:27:408-20.
- Weng MK, Natarajan K, Scholz D, Ivanova VN, Sachinidis A, Hengstler JG, et al. Lineage-specific regulation of epigenetic modifier genes in human liver and brain. *PLoS One.* 2014;9(7):e102035.
- Zimmer B, Pallocca G, Dreser N, Foerster S, Waldmann T, Westerhout J, et al. Profiling of drugs and environmental chemicals for functional impairment of neural crest migration in a novel stem cell-based test battery. *Arch Toxicol.* 2014;88:1109-26.