Archives of Toxicology (2018) 92:3609–3610
https://doi.org/10.1007/s00204-018-2357-y

EDITORIAL

Highlight report: Stem cell-based developmental toxicity tests

Florian Seidel[1]

Received: 15 November 2018 / Accepted: 19 November 2018 / Published online: 26 November 2018

Developmental toxicity testing is a particularly challenging field of toxicology (Colaianna et al. 2013, 2017; Leist et al. 2017; Zimmer et al. 2014). Up to 50% of the animals used for testing in the context of REACH have been estimated to be required for evaluation of developmental and reproductive toxicity (Seiler et al. 2011). Therefore, there is a demand for accurate and fast in vitro tests of this form of toxicity (Shinde et al. 2015; Meganathan et al. 2015; Reif 2015; Weng et al. 2014). Recently, several test systems have been established based on human embryonic stem cells (hESC) that differentiate to neuronal precursor cells (Krug et al. 2013; Kuegler et al. 2012; Weng et al. 2012; Balmer et al. 2012, 2014; Pallocca et al. 2016). Alternatively, multilineage differentiation into ecto-, meso- and endoderm can be recapitulated in vitro (Jagtap et al. 2011; Krug et al. 2013; Meganathan et al. 2012). During the differentiation period large numbers of genes (named 'developmental genes') are either up- or downregulated. The principle of many assays is to study whether test compounds influence expression of these genes compared to solvent controls. Concentration-dependent experiments with the developmental toxicant valproic acid have shown that three concentration ranges can be differentiated: a concentration range of tolerance, where the test compound does not influence expression of any gene; a concentration range of deregulation, where expression of genes is altered but no cytotoxicity occurs; and finally a concentration range of cytotoxicity, where expression of additional cell death associated genes is observed (Waldmann et al. 2014, 2017). Patterns of deregulated genes have been shown to be compound specific. It has, for example, been shown that histone deacetylase inhibitors can be identified by a classifier based on eight genes and can be differentiated from other classes of compounds, e.g., mercurials (Rempel et al. 2015). For quantification of the effect of test compounds, a concept of two indices, 'developmental potency' and 'developmental index', has been established (Shinde et al. 2017). The developmental potency is the fraction of all developmental genes (genes up- or downregulated in spontaneously differentiating cells) that are up- or downregulated by a test compound. The developmental index is the ratio of overrepresentation of developmental genes among all genes deregulated by a test compound (Shinde et al. 2017). Using the developmental index allows a particularly sensitive hazard identification, because some developmental toxicants deregulate expression of only a small number of genes but a high fraction of them are developmental genes (Shinde et al. 2017). Although many developmental toxicity test systems used hESC, recent work has shown that also induced pluripotent stem cells (hiPSC), which are not facing ethical issues such as hESC, allow the identification of developmental toxicants in a similar way (Shinde et al. 2016). However, until now the sensitivity and specificity are major limitations and the future challenges of human stem cell-based developmental toxicity tests. To determine both, analysis of large numbers of positive and negative control compounds (which do versus do not induce developmental toxicity in humans) should be tested at concentrations relevant for the human in vivo situation.

Much progress has already been achieved but there is still a long way to go until in vitro assays will replace animal tests of developmental toxicity.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

References

Balmer NV, Weng MK, Zimmer B et al (2012) Epigenetic changes and disturbed neural development in a human embryonic stem cell-based model relating to the fetal valproate syndrome. Hum Mol Genet 21(18):4104–4114. https://doi.org/10.1093/hmg/dds239

✉ Florian Seidel
seidelf@ifado.de

[1] IfADo, Leibniz Research Centre for Working Environment and Human Factors at TU Dortmund, Ardeystr. 67, 44139 Dortmund, Germany

Balmer NV, Klima S, Rempel E et al (2014) From transient transcriptome responses to disturbed neurodevelopment: role of histone acetylation and methylation as epigenetic switch between reversible and irreversible drug effects. Arch Toxicol 88(7):1451–1468. https://doi.org/10.1007/s00204-014-1279-6

Colaianna M, Schiavone S, Zotti M et al (2013) Neuroendocrine profile in a rat model of psychosocial stress: relation to oxidative stress. Antioxid Redox Signal 18(12):1385–1399. https://doi.org/10.1089/ars.2012.4569

Colaianna M, Ilmjärv S, Peterson H et al (2017) Fingerprinting of neurotoxic compounds using a mouse embryonic stem cell dual luminescence reporter assay. Arch Toxicol 91(1):365–391. https://doi.org/10.1007/s00204-016-1690-2

Jagtap S, Meganathan K, Gaspar J et al (2011) Cytosine arabinoside induces ectoderm and inhibits mesoderm expression in human embryonic stem cells during multilineage differentiation. Br J Pharmacol 162(8):1743–1756. https://doi.org/10.1111/j.1476-5381.2010.01197.x

Krug AK, Kolde R, Gaspar JA et al (2013) Human embryonic stem cell-derived test systems for developmental neurotoxicity: a transcriptomics approach. Arch Toxicol 87(1):123–143. https://doi.org/10.1007/s00204-012-0967-3

Kuegler PB, Baumann BA, Zimmer B, Keller S, Marx A, Kadereit S, Leist M (2012) GFAP-independent inflammatory competence and trophic functions of astrocytes generated from murine embryonic stem cells. Glia 60(2):218–228. https://doi.org/10.1002/glia.21257

Leist M, Ghallab A, Graepel R et al (2017) Adverse outcome pathways: opportunities, limitations and open questions. Arch Toxicol 91(11):3477–3505. https://doi.org/10.1007/s00204-017-2045-3 **(review)**

Meganathan K, Jagtap S, Wagh V et al (2012) Identification of thalidomide-specific transcriptomics and proteomics signatures during differentiation of human embryonic stem cells. PLoS One 7(8):e44228. https://doi.org/10.1371/journal.pone.0044228

Meganathan K, Jagtap S, Srinivasan SP et al (2015) Neuronal developmental gene and miRNA signatures induced by histone deacetylase inhibitors in human embryonic stem cells. Cell Death Dis 6:e1756. https://doi.org/10.1038/cddis.2015.121

Pallocca G, Grinberg M, Henry M et al (2016) Identification of transcriptome signatures and biomarkers specific for potential developmental toxicants inhibiting human neural crest cell migration. Arch Toxicol 90(1):159–180. https://doi.org/10.1007/s00204-015-1658-7

Reif R (2015) Expression classifiers for developmental toxicants. EXCLI J 14:1291–1293. https://doi.org/10.17179/excli2015-765 **(eCollection 2015. No abstract available)**

Rempel E, Hoelting L, Waldmann T et al (2015) A transcriptome-based classifier to identify developmental toxicants by stem cell testing: design, validation and optimization for histone deacetylase inhibitors. Arch Toxicol 89(9):1599–1618. https://doi.org/10.1007/s00204-015-1573-y

Seiler A, Oelgeschläger M, Liebsch M, Pirow R, Riebeling C, Tralau T, Luch A (2011) Developmental toxicity testing in the 21st century: the sword of Damocles shattered by embryonic stem cell assays? Arch Toxicol 85(11):1361–1372. https://doi.org/10.1007/s00204-011-0767-1

Shinde V, Stöber R, Nemade H, Sotiriadou I, Hescheler J, Hengstler J, Sachinidis A (2015) Transcriptomics of hepatocytes treated with toxicants for investigating molecular mechanisms underlying hepatotoxicity. Methods Mol Biol 1250:225–240. https://doi.org/10.1007/978-1-4939-2074-7_16

Shinde V, Perumal Srinivasan S, Henry M et al (2016) Comparison of a teratogenic transcriptome-based predictive test based on human embryonic versus inducible pluripotent stem cells. Stem Cell Res Ther 7(1):190. https://doi.org/10.1186/s13287-016-0449-2

Shinde V, Hoelting L, Srinivasan SP et al (2017) Definition of transcriptome-based indices for quantitative characterization of chemically disturbed stem cell development: introduction of the STOP-Tox_{ukn} and STOP-Tox_{ukk} tests. Arch Toxicol 91(2):839–864. https://doi.org/10.1007/s00204-016-1741-8

Waldmann T, Rempel E, Balmer NV et al (2014) Design principles of concentration-dependent transcriptome deviations in drug-exposed differentiating stem cells. Chem Res Toxicol 27(3):408–420. https://doi.org/10.1021/tx400402j

Waldmann T, Grinberg M, König A et al (2017) Stem cell transcriptome responses and corresponding biomarkers that indicate the transition from adaptive responses to cytotoxicity. Chem Res Toxicol 30(4):905–922. https://doi.org/10.1021/acs.chemrestox.6b00259

Weng MK, Zimmer B, Pöltl D et al (2012) Extensive transcriptional regulation of chromatin modifiers during human neurodevelopment. PLoS One 7(5):e36708. https://doi.org/10.1371/journal.pone.0036708

Weng MK, Natarajan K, Scholz D et al (2014) Lineage-specific regulation of epigenetic modifier genes in human liver and brain. PLoS One 9(7):e102035. https://doi.org/10.1371/journal.pone.0102035 **(eCollection 2014)**

Zimmer B, Pallocca G, Dreser N et al (2014) Profiling of drugs and environmental chemicals for functional impairment of neural crest migration in a novel stem cell-based test battery. Arch Toxicol 88(5):1109–1126. https://doi.org/10.1007/s00204-014-1231-9. 2