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STEM CELLS TEST - RECOMMENDATION OF ECVAM FOR CHEMICAL TESTING WITH CONSEQUENCE IN HEALTH RISK ASSESSMENT

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ABSTRACT. The introduction of stem cells in environmental health studies could mean an important step in health risk assessment. It may be all the more important as we attend to increase the environmental influences to disease -associated epigenetic changes among adults, but especially for children. The assessment of health risk requires testing of environmental chemicals which they continued to need more time in animal studies. The stem cells -human models, increase the rate of testing, that does not require dose translation across species. Validation of environmental exposure will be done for very large interval data, for many chemicals or "chemicals cocktails" at much lower costs.

Key words: *stem cells, alternative methods, chemical testing.*

STEM CELLS DIFFERENTIATION - WHERE, WHEN, HOW?

The epigenetic changes are the molecular basis for long-term effects of the environment on disease development (Ospelt and Gay, 2014). For example, methylation or demethylation related the cells exposure; modulate the expression of CXCL12 with consequence on CpG nucleotides methylation - significantly correlated in the mRNA expression (Karouzakis et al., 2011).

The study of environmental health on "single cells" -like stem cells, gives us the chance to understand more precisely how environmental factors interact with genetic ones.

Stem cells are cells with high capacity of multiplication in particular conditions. These cells are capable to differentiate in a wide variety of other cells, which is why they are also called pluripotent cells. The first stem cells have been observed in the mouse embryonic extract in 1980, but the effective its isolation was performed latest in 1998. Then, for the first time was observed their ability to transform themselves into a variety of specialized cells. The epigenetic landscape during the cells development is the emergence of different cells lineage (Aiba et al., 2009).

Thus can be obtained the liver cells, the kidney cells, cardiomyocytes, neural cells, etc., which are generally difficult to grow in the laboratory using conventional techniques. Stem cells can divide symmetrically and produce other stem cells or can divide asymmetrically producing the cells with very well determined fate. The switch between the two paths and the involved mechanisms are still not well understood, figure 1.

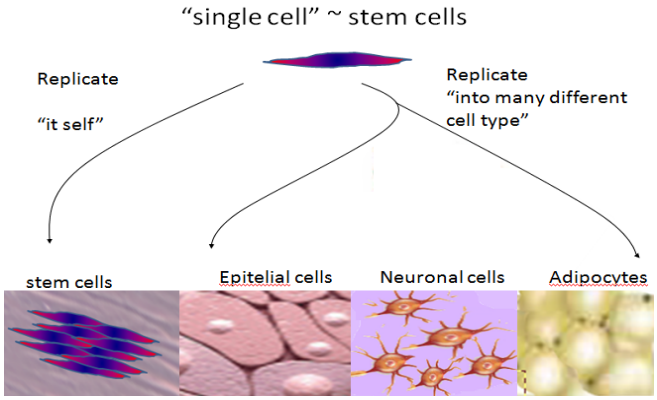

Fig.1. *Symmetric and asymmetric multiplication of stem cells*

In present, we are at the moment of awareness the relevant interaction genes-environment, in other words epigenetics effects on human stem cells model trying to understand how these cells can be involved to define the sensitivities, the susceptibility age dependent or differential population (Casado et al., 2011; Gasiewicz et al., 2017).

Testing of toxicity using stem cells is already in use for different types of exposures.

In chemical exposure, highest interest was in changing the cells contractility due to direct effect of the substance on stem cells. Looking at the cardiomyocytes obtained after the rabbit stem cells differentiation Yazawa et al. (2011), observed that chemical compounds inducing arrhythmia and with effect on electric signal transmission through Purkinje network has similar effect on differentiated cells, when contractility was tested through similar method with those measuring the heart function.

The answer of differentiated stem cells to a wide range of neurotoxic compounds has been studied on neurons, (Betts, 2010) and glial cells to which increase the incidence of autism (Dolmetsch and Geschwind, 2011).

The toxicity of chemical "cocktails" has been also followed on stem cells.

Tox 21, is the program by which the chemicals are tested to improve environmental health and pharmaceutical safety. The following direction could be of interest: cell line selection for high throughput transcriptomics (HTT); profiling environmental, drug, and food-related chemicals that inhibit acetylcholinesterase activity; predictive modeling of developmental toxicity with human pluripotent stem cells; toxicodynamic variability in developmental neurotoxicity; performance based validation of alternative test systems and models; retrofitting existing Tox21 high-throughput screening assays with metabolic capability; expansion of pathway coverage by Tox21 high-throughput screening assays for better prediction of adverse drug effects; development of high-throughput assays to detect chemicals with the potential to induce skin sensitization, eye irritation, or corrosion (EPA, 2017;Thomas et al., 2018).

According with the Interagency Coordinating Committee on the Validation of Alternative Methods, the validation of stem cells used as model will be in comparison with the most relevant current methods, based on the knowledge of human physiology.

Stem cells damage is followed in many other studies based on the inducing of oxidative stress in correlation with xenobiotics metabolism network. The magnitude of apoptosis, cells differentiation in relation with xenobiotics removing has been done (Cieślar-Pobuda et al., 2017).

The advantages of toxicity studies in correlation with cell biology methods focused on end points and stages of life, are presented by Committee on Toxicity Testing and Assessment of Environmental Agents, NRC (2007).

A very important aspect in the future, in toxicology will be to use human cell line-stem cells and cells components, for chemical testing. Testing of chemical teratogenity has been already validated on mouse, embryonic stem cells and is included in screening programs (Ahr et al., 2008; Paquette et al., 2008).

ToxCast neurotoxicity program, EPA's Endocrine Disruption Screening Program (EDSP) has in study thousands of chemicals - with biological activity, and generates data and predictive models on thousands of chemicals using stem cells.

CONCLUSIONS

In conclusion, if the effect of environmental factors on human is analyzed today from perspective of the observed effects on human health, interesting for the future would be the examination of stem cells and respectively, its differentiation process like model for different kind of exposures. End points will be particularly to exposure mark; so it will be different for indoor ambient pollutants -lung exposure, compared with ingested xenobiotics - liver exposure, or stored organchlorinated compounds - fatty tissues exposure, etc. In all these situations must be, included the cell's answer due to exposure sensitivities and individual susceptibility for assessing the real human health risk.

REFERENCES

Ahr H.J., Alepée N., Breier S., Brekelmans C., Cotgreave I., Gribaldo L., Negro G.D., De Silva O., Hartung T., Lacerda A., Leblanc B., Lecerf C., Linge J.P., Louhimies S., Manou I., Maxwell G., Müller K.K., Pape W., Redhead K., Schröder K.R., Sladowski D., Van der Jagt K., Vanparys P., 2008, Barriers to Validation: A Report by European Partnership for Alternative Approaches to Animal Testing (EPAA) Working Group 5a. *Alternatives to Laboratory Animals,* **36** (4), pp. 459-464.

Aiba K., Nedorezov T., Piao Y., Nishiyama A., Matoba R., Sharova L.V., Sharov A.A., Yamanaka S., Niwa H., Ko M.S., 2009, Defining developmental potency and cell lineage trajectories by expression profiling of differentiating mouse embryonic stem cells. *DNA Research*, **16** (1), pp. 73–80.

Betts K.S., 2010, Using Stem Cells to Study Developmental Neurotoxicology. *Environmental Health Perspectives*, **118** (1), pp. 433-437.

Casado F.L., Singh K.P., Gasiewicz T.A., 2011, Aryl hydrocarbon receptor activation in hematopoietic stem/progenitor cells alters cell function and pathway-specific gene modulation reflecting changes in cellular trafficking and migration. *Molecular Pharmacology Fast Forward*, **80** (4), pp. 673–682.

Cieślar-Pobuda A., Yue J., Lee H.C., Skonieczna M., Wei Y.H., 2017, ROS and Oxidative Stress in Stem Cells. *Oxid Med Cell Longev*, Article ID 5047168, DOI: 10.1155/2017/5047168.

Dolmetsch R., Geschwind D.H., 2011, The human brain in a dish: the promise of iPSC-derived neurons. *Cell.,* **145** (6), pp. 831–834.

EPA Web Archive, January 19, 2017, Toxicity Forecasting, Advancing the Next Generation of Chemical Evaluation.

Gasiewicz TA.,Singh KP., Cassado FL., 2017, Aryl Hydrocarbon Receptor and Stem Cells, Hidawi Stem Cell International, Volume 2017, Article ID 4602854, https://doi.org/10.1155/2017/4602854

Karouzakis E., Rengel Y., Jungel A. et al., 2011, DNA methylation regulates the expression of CXCL12 in rheumatoid arthritis synovial fibroblasts. *Genes Immun*, **12**, pp. 643–652.

NRC (National Research Council), 2007, *Committee on Toxicity Testing and Assessment of Environmental Agents, National Research Council: Toxicity Testing in the 21st Century: A Vision and a Strategy*. The national academies press. 196 p. Available at http://www.nap.edu/catalog.php?record_id=11970, accessed on February 2020.

Ospelt C., Gay S., 2014, Epigenetics in inflammatory systemic diseases. *Der Internist*, **55** (2), pp. 124-127.

Paquette J.A., Kumpf S.W., Streck R.D., Thomson J.J., Chapin R.E., Stedman D.B., 2008, Assessment of the Embryonic Stem Cell Test and application and use in the pharmaceutical industry. *Birth Defects Res. B Dev. Reprod. Toxicol.*, **83**, pp. 104-111.

Thomas R.T., Paules R.S., Simeonov A., Fitzpatrick S., Crofton K., Casey W., Mendrick D., 2018, The US Federal Tox21 Program: A Strategic and Operational Plan for Continued Leadership. *ALTEX*, **35** (2), pp. 163-168.

Yazawa M., Hsueh B., Jia X., Pasca A.M., Bernstein J.A., Hallmayer J., Dolmetsch R.E., 2011, Using induced pluripotent stem cells to investigate cardiac phenotypes in Timothy syndrome. *Nature*, **471** (7337), pp. 230-234.