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Guest editorial:

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

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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.

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