Toxicogenomics directory of chemically exposed human hepatocytes.

Grinberg M, Stöber RM, Edlund K, Rempel E, Godoy P, Reif R, Widera A, Madjar K, Schmidt-Heck W, Marchan R, Sachinidis A, Spitkovsky D, Hescheler J, Carmo H, Arbo MD, van de Water B, Wink S, Vinken M, Rogiers V, Escher S, Hardy B, Mitic D, Myatt G, Waldmann T, Mardinoglu A, Damm G, Seehofer D, Nüssler A, Weiss TS, Oberemm A, Lampen A, Schaap MM, Luijten M, van Steeg H, Thasler WE, Kleinjans JC, Stierum RH, Leist M, Rahnenführer J, Hengstler JG (2014) Toxicogenomics directory of chemically exposed human hepatocytes. *Arch Toxicol* 88(12), 2261-2287.

Abstract

A long-term goal of numerous research projects is to identify biomarkers for in vitro systems predicting toxicity in vivo. Often, transcriptomics data are used to identify candidates for further evaluation. However, a systematic directory summarizing key features of chemically influenced genes in human hepatocytes is not yet available. To bridge this gap, we used the Open TG-GATES database with Affymetrix files of cultivated human hepatocytes incubated with chemicals, further sets of gene array data with hepatocytes from human donors generated in this study, and publicly available genome-wide datasets of human liver tissue from patients with non-alcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular cancer (HCC). After a curation procedure, expression data of 143 chemicals were included into a comprehensive biostatistical analysis. The

results are summarized in the publicly available toxicotranscriptomics directory (http://wiki.toxbank.net/toxicogenomics-map/) which provides information for all genes whether they are up- or downregulated by chemicals and, if yes, by which compounds. The directory also informs about the following key features of chemically influenced genes: (1) Stereotypical stress response. When chemicals induce strong expression alterations, this usually includes a complex but highly reproducible pattern named 'stereotypical response.' On the other hand, more specific expression responses exist that are induced only by individual compounds or small numbers of compounds. The directory differentiates if the gene is part of the stereotypical stress response or if it represents a more specific reaction. (2) Liver disease-associated genes. Approximately 20 % of the genes influenced by chemicals are up- or downregulated, also in liver disease. Liver disease genes deregulated in cirrhosis, HCC, and NASH that overlap with genes of the aforementioned stereotypical chemical stress response include CYP3A7, normally expressed in fetal liver; the phase II metabolizing enzyme SULT1C2; ALDH8A1, known to generate the ligand of RXR, one of the master regulators of gene expression in the liver; and several genes involved in normal liver functions: CPS1, PCK1, SLC2A2, CYP8B1, CYP4A11, ABCA8, and ADH4. (3) Unstable baseline genes. The process of isolating and the cultivation of hepatocytes was sufficient to induce some stress leading to alterations in the expression of genes, the so-called unstable baseline genes. (4) Biological function. Although more than 2,000 genes are transcriptionally influenced by chemicals, they can be assigned to a relatively small group of biological functions, including energy and lipid metabolism, inflammation and immune response, protein modification, endogenous and xenobiotic metabolism, cytoskeletal organization, stress response, and DNA repair. In conclusion, the introduced toxicotranscriptomics directory offers a basis for a rationale choice of candidate genes for biomarker evaluation studies and represents an easy to use source of background information on chemically influenced genes.

Beteiligte Forschungseinheiten

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