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Data Article

Data on novel DNA methylation changes induced by valproic acid in human hepatocytes

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ABSTRACT

Valproic acid (VPA) is a widely prescribed antiepileptic drug in the world. Despite its pharmacological importance, it may cause liver toxicity and steatosis. However the exact mechanism of the steatosis formation is unknown. The data presented in this DIB publication is used to further investigate the VPA-induced mechanisms of steatosis by analyzing changes in patterns of methylation. Therefore, primary human hepatocytes (PHHs) were exposed to VPA at a concentration which was shown to cause steatosis without inducing overt cytotoxicity. VPA was administered for 5 days daily to PHHs. Furthermore, after 5 days VPA-treatment parts of the PHHs were followed for a 3 days washout. Differentially methylated DNA regions (DMRs) were identified by using the 'Methylated DNA Immuno-Precipitation - sequencing' (MeDIP-seq) method. The data presented in this DIB demonstrate induced steatosis pathways by all DMRs during VPA-treatment, covering interesting drug-induced steatosis genes (persistent DMRs upon terminating VPA treatment and the *EP300* network). This was illustrated in our associated article (Wolters et al., 2017) [1]. MeDIP-seq raw data are available on ArrayExpress (accession number: E-MTAB-4437).

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Specifications Table

Subject area	*Biology*
More specific subject area	*(Hepato)toxicogenomics*
Type of data	*Figure and Tables*
How data was acquired	*Illumina HiSeq. 2000 sequencer*
Data format	*Differentially methylated DNA regions/genes, pathways, statistical analysis*
Experimental factors	*Primary human hepatocytes (PHHs) were treated by valproic acid (VPA) at an incubation concentration of 15 mM for 5 days daily followed by a washout of 3 days*
Experimental features	*The treated samples were corrected for time-matched vehicle controls. The persistent changes were identified by determining DNA methylation similarities between samples of 5 days daily VPA-treatment and samples of 3 days washout upon the 5 days daily VPA-treatment*
Data source location	*Department of Toxicogenomics, Maastricht University, the Netherlands*
Data accessibility	*Methylated DNA Immuno-Precipitation – sequencing (MeDIP-seq) raw data are available on ArrayExpress (accession number: E-MTAB-4437).*

Value of the Data

- The data derived from primary human hepatocytes (PHHs) treated with valproic acid (VPA) as well as the data analysis approaches in this publication can serve as a benchmark to investigate the epigenetics effects of other hepatotoxic compounds, since the data show that Methylated DNA Immuno-Precipitation – sequencing (MeDIP-seq) analysis is highly informative in disclosing novel mechanisms of VPA-induced toxicity in PHHs.
- The investigation of persistent methylation changes in PHHs provides a new perspective for other studies related to the drug-induced steatosis or other forms of toxicity.
- The listed gene *EP300* together with the neighbors, of the network analysis, can be used for the development of biomarker screening tools for the early detection of drug-induced steatosis or other forms of toxicity, also by using other cell types.

1. Data

Methylated DNA Immuno-Precipitation – sequencing (MeDIP-seq) analysis showed that the methylation of more than 6000 genes significantly changed after 5 days daily valproic acid (VPA)-treatment (3006 hypermethylated differentially methylated DNA regions (DMRs) and 3077 hypomethylated DMRs). 31 DMRs were persistently methylated after taking the compound away (11 hypomethylated DMRs and 20 hypermethylated DMRs). The names and functions of those persistent DMRs are shown in Table 1. Furthermore, the 3006 hypermethylated and 3077 hypomethylated DMRs were classified into 119 significantly enriched pathways (Table 2). The unique genes of all those 119 significantly enriched pathways, which have shown significant methylation changes in our data after 5 days daily VPA-treatment, formed a complex network module (Fig. 1A-B). The gene *EP300* has 33 neighbors (Fig. 1B-C) and the gene names, gene symbols, and fold changes (FCs) of those neighbors were shown in Table 3. A more detailed description of those findings can be found in Wolters et al. [1].