



THE CROSS-TALK OF THE HEPATIC CHOLESTEROL AND DRUG METABOLISM TRANSCRIPTOME

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Liver is the major organ of endobiotic and xenobiotic metabolism that has to adapt timely to a variety of endogenous and exogenous stimuli. Drugs that are used to treat human diseases can at the same time be toxic to the liver. With particular emphasis on interactions between cholesterol homeostasis and drug metabolism we investigate the transcriptome of mouse livers and human primary hepatocytes that are treated by cholesterol lowering drugs and by drugs that serve as models for induction of nuclear receptors CAR and PXR. Using expression profiling by dedicated Steroltalk microarrays we identified most modulated pathways of the mouse liver after cholesterol diet and TCPOBOP. While diet represses cholesterol synthesis, TCPOBOP re-activates expression in cholesterol loaded conditions. This up-regulation is SREBP-independent and CAR-dependent in the mouse. Sterol and lipoprotein analyses revealed an increase in cholesterol synthesis but a drop of liver and serum cholesterol due to increase in bile acid metabolism and up-regulated removal of LDL. Expression profiling with Steroltalk and Affymetrix arrays on hepatocytes from 7 human donors shows that statins induce extensive transcriptome changes. After 24h, atorvastatin and rosuvastatin modulated expression of 30 and 97 genes, and after 48h, 2095 and 2064 genes, respectively. The common statin effect is represented by 185 genes that are modulated in both time points. Many of these genes are activated by nuclear receptors CAR and transcription factors of the SREBP family. Due to enrichment of cholesterol and drug metabolism genes on the Steroltalk chip, different KEGG pathways were presented in Affymetrix and Steroltalk data sets. Informatic and data mining analyses are in progress and will be presented at the meeting. Conclusions: Using expression profiling combined by sterol metabolite studies, gene set enrichment analysis and other data mining approaches, we show how xenobiotics (TCPOBOP, rifampicin, atorvastatin, rosuvastatin) and high cholesterol diet influence the hepatic transcriptome. We explain for the first time mechanisms for some of the drug effects and pinpoint novel side effects. Acknowledgements: A part of this work was performed in collaboration with partners of the FP6 project STEROLTALK, K. Monostory, J.M. Pascussi, U.A. Meyer and I. Bjorkhem.