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Microarray Analysis Of Hepatic Gene Expression In Liver-Specific NADPH-Cytochrome P450 Reductase (Cpr)-Knockout And Global Cpr-Knockdown Mouse Models

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Our aim was to identify genetic bases for observed phenotypes in two mutant mouse models, Cpr-low, with globally decreased CPR expression, and liver-Cpr-null, with liver-specific deletion of the Cpr gene; the phenotypes include a reduced serum cholesterol and an induction of hepatic cytochrome P450s (CYP) in both strains, and hepatomegaly and fatty liver in the liver-Cpr-null mice. Microarray analysis of hepatic gene expression revealed that multiple enzymes in the cholesterol biosynthetic pathways were induced; however, their induction was apparently insufficient to maintain cholesterol homeostasis, in the absence of adequate levels of hepatic CPR expression in either mouse strains. On the other hand, although there was altered expression of enzymes for fatty acid synthesis and oxidation in both strains, induction of a lipid transporter (CD36) was only detected in the liver-Cpr-null mouse, which may have led to the observed liver pathology in this strain. Furthermore, we found increased expression of many biotransformation enzymes in both liver-Cpr-null and Cpr-low mice, which implies a critical need for these enzymes to maintain homeostasis of numerous endogenous substrates. The anticipated accumulation of these compounds is likely responsible for the induction of microsomal CYPs and other biotransformation enzymes. (Supported in part by NIH grant CA92596)

