S11-4 Development of chimeric mice with human hepatocytes and their characters

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We transplanted human hepatocytes into albumin enhancer/promoter-driven urokinase-type plasminogen activator-transgenic SCID mice (uPA/SCID mice), immunodeficient mice with liver failure, and produced human hepatocyte-chimeric mice with livers replaced by more than 70% with human hepatocytes. Histological examinations revealed that the human hepatocytes in the chimeric mouse livers were lined with sinusoids constructed with mouse liver non-parenchymal cells (sinusoidal endothelial cells, hepatic stellate cells, and Kupffer cells) and MRP2 protein expressing bile canaliculi were also observed between the human hepatocytes. The Gene expression levels of the human hepatocytes in the chimeric mouse liver were compared with those in the human liver by microarray analysis. Approximately eighty-five percent of all genes including phase I and II metabolic enzymes, transporters and other metabolic enzymes were expressed at similar levels in the chimeric mouse liver as in the human liver. Similar to normal human liver, the Cytochrome P450 (CYP) 1A2 and CYP3A4 protein expression was observed only in the pericentoral hepatocytes. The chimeric mouse liver retained a similar CYP activity to the human liver, and the CYP mRNAs, proteins, and enzyme activities could be induced in the chimeric mouse liver treated with CYP specific inducers. From these results we conclude that the chimeric mice should be a useful animal model for predicting human-type metabolism, efficacy and toxicity of new chemical entities