Detection of human hepatic toxicity in chimeric mice with humanized liver by human ALT1 ELISA system

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To predict human (h-) hepatic toxicity a suitable animal model is needed because some medicines or chemical entities confirmed to be safe in experimental animals are toxic to the h-liver. We developed chimeric mice with h-hepatocytes (PXB-mice®), which have been used for Drug Metabolism and Pharmacokinetics (DMPK) studies and hepatitis B or C virus (HBV or HCV)-infection studies, to predict h-metabolism and chemical efficacy for HBV or HCV. Since >70% of the PXB-mice livers are repopulated with h-hepatocytes as well as <30% mouse (m-) hepatocytes, whether m- or h-hepatocytes are the cause of a chemical-induced increase in ALT activity cannot be distinguished. ALT1 and ALT2 are isotypes of ALT; the former is a cytoplasmic protein and the latter is a mitochondrial protein with indistinguishable enzyme activity. Therefore, to identify h-specific hepatotoxicity, we produced h-ALT1-specific antibodies not crossed with m-ALT1, m-ALT2, or h-ALT2 by immunization with recombinant h-ALT1 protein synthesized by Baculovirus. Using 2 types of h-ALT1 antibodies we developed a h-ALT1 sandwich ELISA system, and detected h-ALT1 protein in PXB-mouse plasma. PXB- and SCID mice were administered aflatoxin B1 (AFB-1) or CCl_4 orally for 7 days, and the ALT activities and h-ALT1 concentrations in plasma were measured periodically. ALT activity was found to be higher in the AFB-1-treated PXB-mice than the AFB-1-treated SCID mice, and the kinetics of ALT activity was similar to h-ALT1 protein levels in the PXB-mice. Conversely, ALT activity was higher in the CCl_4-treated SCID mice than the CCl_4-treated PXB-mice, and the kinetics of ALT activity was different from h-ALT1 levels in the PXB-mice. Therefore, AFB-1 and CCl_4 are more toxic for h-hepatocytes and m-hepatocytes, respectively. In conclusion, using the h-ALT1 ELISA system, h-specific hepatic toxicity was detected quantitatively in the PXB-mice.