IN VITRO EVALUATION OF DRUG-INDUCTION OF mRNA OF HUMAN DRUG-METABOLIZING ENZYMES USING HEPATOCYTES ISOLATED FROM CHIMERIC MICE BEARING HUMAN HEPATOCYTES

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Chimeric mice with nearly 80% humanized liver were constructed by transplantation of human hepatocytes. Hepatocytes were isolated from chimeric mice (replacement index from mouse liver to human liver: about 80%) and cryopreserved. We investigated the mRNA induction of human drug-metabolizing enzymes in primary cultures of these chimeric mouse hepatocytes. The enzyme inducers used in this study were β-naphthoflavone (β-NF) and rifampicin (RIF). Analysis was performed by a quantitative real-time RT-PCR method using primers and TaqMan probe by which the selectivity was validated for interspecies and target genes. The CYP1A2 and CYP3A4 mRNA levels were increased several-fold by 25-μM exposure to β-NF and 50-μM exposure to RIF as compared with untreated controls. Further, we will discuss in detail the relationship between the chimeric mouse hepatocytes and the respective donor hepatocytes in forms of the mRNA induction of drug-metabolizing enzymes. In conclusion, the results of the present study demonstrated that the primary culture of hepatocytes isolated from the near-completely humanized mouse liver was useful as those from human liver for evaluating the induction of drug-metabolizing enzymes in human. This in vitro study will enable the estimation of ADME in humans in the development of new medicines.