MS09-6 Functional characterization of human and cynomolgus monkey UGT enzymes

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UDP-glucuronosyltransferases (UGTs) play important roles in conjugating numerous xenobiotics and endogenous substances. UGT1A1 and UGT1A6, mainly expressed in the livers, are enzymes of major toxicological interest because they metabolize various drugs and environmental chemicals. In this symposium, I report the enzymatic properties of UGT1A1 and UGT1A6 of humans and cynomolgus monkeys, and discuss the species differences in UGT1A functions among primates. UGT1A1 and UGT1A6 cDNAs of humans and cynomolgus monkeys were cloned, and the corresponding proteins were expressed in insect or yeast cells. The function of UGT1A1 and UGT1A6 enzymes were characterized by kinetic analysis of SN-38 and serotonin glucuronidation, respectively. SN-38 glucuronidation by human and cynomolgus monkey UGT1A1s showed sigmoidal kinetics, and the S_{50} and V_{max} values were similar between humans and cynomolgus monkeys. In serotonin glucuronidation, the kinetics of human and cynomolgus monkey UGT1A6s were fitted to the Michaelis-Menten model, showing that the V_{max} value of cynomolgus monkey UGT1A6 was significantly lower (about 15%) than that of human UGT1A6. These findings suggest that the profile for species difference in the function of primate UGT1As markedly differs among UGT isoforms. Information gained in our studies should help with *in vivo* extrapolation and assessment of the toxicity of xenobiotics.