HETERO-DIMERIC FORMATION OF HUMAN UDP-GLUCURONOSYLTRANSFERASES IN HEPATIC AND cDNA-EXPRESSED YEAST MICROSOMES
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UDP-glucuronosyltransferase (UGT)-dependent glucuronidation towards xenobiotics and endobiotics is known to have complex regulatory properties in microsomal membranes. UGT can interact to form homo- and heterodimer and the interaction may play a role in the regulation of the glucuronidation including modulation of substrate selectivity (Ishii et al, Mol. Pharmacol. 2001, 60, 1040-1048). We have previously indicated the hetero-dimeric formation between UGT1As and UGT2B1 in rat hepatic microsomes using UGT isozyme-specific antipeptide antibodies (Ikushiro et al, Biochemistry 1997, 36, 7154-7161). We will focus on the modulation of glucuronidation via oligomeric formation of human UGT isozymes in microsomal membranes. Immunopurification and western blot analysis of human hepatic microsomes using specific antibodies showed that human UGT1A isozymes could interact with UGT2B7 to be the human equivalent of rat UGT2B1, but not other UGT2B isozymes, at least UGT2B15 or 2B17. In order to confirm the interaction, we have cloned human UGT isozyme cDNAs and constructed the co-expression system of human UGT 1A and UGT2B isozymes in yeast. Co-immunoeulation of UGT2B7 with UGT1As clearly showed the specific interaction between human UGT isozymes in yeast microsomes. These data indicate the hetero-dimeric formation of human UGT1A isozymes with UGT2B7, and the specific hetero-dimer has a potential for modulation of UGT1As or UGT2B7-dependent glucuronidating activity. We are currently analyzing the functional implication of hetero-dimerization in different UGT isozymes using the yeast co-expression system.