Induction of UGT1A1 and CYP2B6 by an antimitogenic factor in HepG2 cells is mediated through suppression of CDK2 activity

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HGF is known not only as a potent mitogen for hepatocytes and several types of tumor cells including HuH6, Caco2, and MCF7 cells, but also as an anti-mitogenic factor for some types of tumor cells such as HepG2 cells. HGF increased mRNA and protein levels of UGT1A1 and CYP2B6 as well as the endogenous cycline-dependent kinase (CDK) inhibitors p16, p21, and p27 in HepG2 cells, but not HuH6, Caco2, or MCF7 cells. Treatment with U0126 (an ERK inhibitor) suppressed the HGF-induced expression of UGT1A1 and CYP2B6 as well as p16, p21, and p27 in HepG2 cells. The CDK inhibitor roscovitine also enhanced the expression of UGT1A1, CYP2B6, and CYP3A4. Transfection of anti-CDK2 siRNA led to elevated levels of UGT1A1, CYP2B6, and CYP3A4 in HepG2 and SW480 cells, while anti-CDK4 siRNA did not significantly enhance the expression of these enzymes. CDK2, a key regulator of G1-S cell cycle progression, is activated by Akt-mediated phosphorylation. The inhibition by LY284002 of HGF downstream of the PI3 kinase-Akt signaling pathway led to an increase in the expression of UGT1A1 and CYP2B6, also suggesting the involvement of CDK2 in the HGF-induced expression of UGT1A1 and CYP2B6 in HepG2 cells. In fact, CDK2 activity was decreased in HGF-treated HepG2 cells.

Does CAR or PXR play an essential role in UGT1A1 and CYP2B6 expression in HGF-stimulated HepG2 cells? The CAR protein level not only in the cell lysate but also in the nucleus was reduced after HGF treatment. In addition, the suppression of CAR expression using anti-CAR siRNA did not repress the HGF- and roscovitine-induced expression of UGT1A1 and CYP2B6. Taken together, our results demonstrate that the expression of UGT1A1 and CYP2B6 is negatively regulated through a CDK2 signaling pathway linked to cell cycle progression in HepG2 and SW480 cells, the mechanism of which may differ from that of CYP3A4 expression through PXR phosphorylated by CDK2.