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Transcriptional regulation of *UGT1A1* gene expression and its cell cycle-dependent expression by nuclear receptor CAR

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Human UDP-glucuronosyltransferase (UGT) 1A1 is a critical enzyme responsible for detoxification and metabolism of endogenous and exogenous lipophilic compounds, such as potentially neurotoxic bilirubin and the anticancer drug irinotecan SN-38, via conjugation with glucuronic acid. This study indicates the transcriptional regulation of *UGT1A1* gene expression by nuclear receptors and its cell cycle-dependent expression by CAR.

The 290-bp distal enhancer module (phenobarbital response element, -3499/-3210) fully accounted for the CAR-, PXR-, GR-, and AhR-mediated gene activation of the *UGT1A1* gene. HNF1α bound to the proximal promoter motif not only enhances the basal reporter activity of *UGT1A1*, including the distal (-3570/-3180) and proximal (-165/-1) regions, but also influences the transcriptional regulation of *UGT1A1* by CAR, PXR, GR, and AhR to markedly enhance reporter activities, and T-3279G mutation reduces but does not abolish CAR-, PXR, GR-, and AhR-dependent transcriptional activity of the *UGT1A1* 3570-bp promoter, suggesting that UGT1A1 inducers could be beneficial for preventing the development of mild unconjugated hyperbilirubinemia in individuals with T-3279G.

Next, this study demonstrates cell cycle-dependent expression of UGT1A1. CAR and UGT1A1 proteins accumulate during G1 in human SW480 and HepG2 cells. After the G1/S phase transition, CAR protein levels decreased, and CAR was very low level in cells by the late M phase. CAR expression in both cell lines was suppressed by RNA interference-mediated suppression of CDK4. Depletion of CAR by RNA interference in both cells resulted in decreased UGT1A1 and MDM2 expression that led to p21 upregulation and repression of HepG2 cell growth. Thus, these results demonstrate that CAR expression is an early G1 event regulated by CDK4. These findings suggest that CAR may influence the expression of genes involved in not only the metabolism of endogenous and exogenous substances but also in the cell proliferation.