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Human XREM-CYP3A4 Gene Regulation, Role of Nuclear Receptors in Human Hepatoma Cells

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The cytochrome P450 3A4 is thought to be involved in the metabolism of nearly 50% of all the drugs currently proscribed. Alteration in the activity of CYP3A4 seems to be a key of drug responsiveness and toxicity. In order to gain the insight of the molecular mechanism of CYP3A4 gene expression, study has been undertaken to investigate the regulation of CYP3A4 gene expression by proximal promoter in human hepatoma HepG2 cells. HepG2 cells were transfected with a plasmid pCYP3A4-Luc containing ~1kb of the CYP3A4 proximal promoter region (-863 to +64 bp) and XREM(xenobiotic response enhancer module) in front of a reporter gene, luciferase, in the presence or absence of pSAP-SXR. In HepG2 cells, CYP3A4 inducers, such as rifampicin, dexamethasone, PCN and RU486 showed minimal stimulation of XREM-CYP3A4 proximal promoter activity in the absence of SXR. 4-Dimethylamino-N-[4-(2-hydroxycarbamoylvinyl)benzyl]benzamide (IN2001), a new class HDAC inhibitor significantly increased CYP3A4-XREM promoter activity over untreated control cells and rifampicin concomitant treatment with IN2001 increased further CYP3A4 proximal promoter activity that was stimulated by IN2001. The results of this study demonstrated that both acetylated histone and SXR are essential to increase of CYP3A4 proximal promoter activity by CYP3A4 inducers such as PCN, rifampicin, and RU486. CYP3A4-XREM activity was increased when SXR or hERα was cotransfected. And we showed that hepatocyte nuclear factor (HNF4a) was critical in the transcriptional activation of CYP3A4-XREM activity. The data suggest that these nuclear receptors play a critical role to increase of CYP3A4 proximal promoter activity and interact competitively. HNF1α and HNF3α did not increase of CYP3A4 gene expression that was inducer. Taken together, these results indicated that the inhibition of histone deacetylation was required to SXR-mediated increase in CYP3A4 proximal promoter region when rifampicin and other inducers were treated. Also this data suggested that HDAC inhibitors seemed to facilitate the CYP3A4 proximal promoter to be activated by chemicals. And ERα and HNF4α seemed to increase the CYP3A4 proximal promoter to be activated by chemicals

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