【P-39】

Regulations of Human CYP3A4-Xrem Promoter Activities in HepG2 and Hepa I Cells.

Jin Young An and Yhun Yhong Sheen and Dae Kee Kim
Department of Pharmacology, ewha womans university

Cytochrome P450 monooxygenase 3A4 (CYP3A4) is responsible for the metabolism of endogenous steroids and drugs in liver. The expression of CYP3A4 gene is induced by a variety of structurally unrelated xenobiotics including the antibiotic rifampicin, pregnenolone 16α-carbonitrile (PCN), and endogenous hormones, that might mediate through steroid and xenobiotic receptor (SXR, HNFs) system. In order to gain the insight of the molecular mechanism of CYP3A4 gene expression, study has been undertaken to investigate if the histone deacetylation is involved in the regulation of CYP3A4 gene expression by proximal promoter with XREM (xenobiotic response enhancer module) distal promoter region in human hepatoma HepG2 cells. Also we have investigated to see if SXR or HNFs is involved in the regulation of CYP3A4-XREM-proximal promoter activityin HepG2 cells. In HepG2 cells, CYP3A4 inducers, such as rifampicin, dexamethason, PCN and RU486 showed minimal stimulation of XREM- CYP3A4 promoter activity in the absence of SXR and histone deacetylase (HDAC) inhibitors. IN 2001, a new class HDAC inhibitor significantly increased CYP3A4-XREM -proximal 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-XREM-proximal promoter activity by CYP3A4 inducers. Also, we show that the orphan nuclear receptor hepatocyte nuclear factor (HNF4a) is critically in transcriptional activation of CYP3A4-XREM-proximal promoter activity. Also this data suggested that HDAC inhibitors seemed to facilitate the CYP3A4-XREM-proximal promoter to be activated by chemicals.

Keyword : CYP3A4