The nuclear receptors PXR and LXR are regulators of the scaffold protein PDZK1

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PDZK1 (NHERF3) interacts with membrane proteins whereby modulating their spatial arrangement, membrane stability, and function. One of the membrane proteins shown to be stabilized by interaction with PDZK1 is the HDL-receptor SR-BI (SCARB1). Testing the influence of TO 901317, a known activator of liver X receptor alpha (LXRα, NR1H3) which is a central regulator of the lipid homeostasis, Grefhorst et al. reported in 2012 that administration of TO 901317 did not affect PDZK1 expression and reduced the amount of SR-BI protein in mouse liver. Considering that TO 901317 also activates the xenosensor pregnane X receptor (PXR, NR1I2), it was aim of this study to further investigate the influence of LXRα and PXR activation on transcription of PDZK1. First, we tested the transactivation of PDZK1 by LXRα or PXR in cell-based reporter gene assays comparing the effect of prototypical ligands to that of TO 901317. Ligand mediated activation of LXRα increased, while that of PXR lowered luciferase activity. Further, we located the most likely binding site for LXRα and PXR on the PDZK1 promoter between -85/bp and -54/bp. The transcriptional regulation by LXRα was further supported showing enhanced mRNA expression of PDZK1 in HepG2 cells treated with the selective LXRα-agonist GW3965, while treatment with TO 901317 reduced the protein amount of PDZK1. Taken together, we provide evidence that both LXRα and PXR are transcriptional regulators of PDZK1 supporting the previous notion that the scaffold protein is part of cholesterol homeostasis and drug metabolism.

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