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Studies on the transcriptional regulation of the scaffolding protein PDZK1

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Regulation of physiological plasma cholesterol levels crucially contribute to lipid homeostasis, thereby preventing the development of atherosclerotic cardiovascular disease. Hepatic handling of cholesterol is realised by the coordinated function of various cell surface receptors and transporters including the hepatic HDL receptor scavenger receptor class B member 1 (SR-BI). Therefore, current research is increasingly focused on regulatory pathway influencing activity, stability and expression of SR-BI. One of the mechanisms recently discussed to be involved in modulation of SR-BI function is the scaffolding protein PDZK1 which is assumed to be regulated by nuclear factors liver X receptor (LXR) and pregnane X receptor (PXR). The aim of the present study was to understand the different roles of the specific LXR agonist GW3965 and the non-specific LXR ligand TO901317 in the transcriptional regulation of PDZK1 and to determine whether these compounds might contribute to a coordinated regulation of hepatic SR-BI function. Cell based reporter gene assays revealed that GW3965 enhanced PDZK1 promotor activity by specific LXR stimulation whereas TO901317 diminished PDZK1 activation by simultaneous LXR and PXR induction. Moreover, we showed that TO901317 mediated reduction of promotor activity may predominantly ascribe to PXR activation. Findings of quantitative real-time PCR experiments and immunoblot analyses supported the different roles of those compounds in the modulation of PDZK1 gene expression following the same trend of regulation. Additionally, we identified that GW3965 and TO901317 slightly increased SR-BI mRNA and protein expression levels. Taken together, our data suggest that both GW3965 and TO901317 regulate PDZK1 and potentially hepatic SR-BI by LXR and PXR induction. Based on these findings, PDZK1 and SR-BI might be components of a physiological network coordinated by nuclear factors LXR and PXR, thereby contributing to physiologic cholesterol homeostasis.