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Activated Farnesoid X receptor by GW4064 protects against renal fibrosis in HK2 cells.

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Objectives : Renal fibrosis is the common pathway of chronic kidney disease progression. Induced SMAD2/3 by transforming growth factor-beta(TGFb) is a critical event in progressive of chronic kidney disease. However, the role of non-SMAD signaling in fibrotic progressing remains unexplored. The nuclear receptor FXR (farnesoid X receptor), a ligand-activated transcriptional factor, may play a pivotal role in renal fibrosis.

Methods : We tested whether activated-FXR by GW4064 protects against renal fibrosis through non-SMAD signaling. To explore anti-fibrotic effects of FXR, we treated with GW4064 in TGFb induced HK2 cells and checked fibrosis marker, fibronectin, CTGF and alpha-SMA. We also examined the phosphorylation level of epidermal growth factor receptor (EGFR) and Src kinase in the identification of anti-fibrosis signals in the treatment of FXR agonists.

Results : TGFb-induced Src kinase and EGFR phosphorylations were decreased by the treatment of FXR synthetic agonist GW4064, while those phosphorylations were not altered by the treatment of chenodeoxycholic acid (CDCA), FXR agonist. TGFb-induced fibronectin, CTGF and alpha-SMA expressions were decreased by GW4064 treatment. Fibronectin, CTGF and alpha-SMA induced by TGFβ decreased markedly at GW4064 and CDCA concentrations of 200 nM and 25 μM, respectively.

Conclusions : These results suggest that activated nuclear receptor FXR by GW4064 has anti-fibrotic effects through regulation of EGFR signaling by inhibition of Src kinase phosphorylation, not SMAD signaling.

Keywords : FXR, Fibrosis