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The role of FXR in kidney autophagy for suppressing renal fibrosis.

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Objectives: Autophagy is an evolutionarily conserved catabolic process that removes damaged organelles and maintains cellular energy homeostasis. Acute regulation by nutrient-sensing of autophagy and long-term transcriptional regulation by nuclear hormone receptor FXR (farnesoid X receptor) is well known. Also, kidney autophagy regulates TGFβ expression and suppresses kidney fibrosis. However, the functional role of FXR on TGFβ-induced kidney autophagy is relatively unknown.

Methods: Expression levels of LC3 protein and autophagy related genes were measured on treatment with TGFβ and FXR agonist GW4064 in human proximal tubule cells (HK2 cells). The LC3 Puncta formation was monitored by fluorescence microscopy. Expression levels of protein and autophagy related genes were measured on down-regulation of FXR by siRNA or FXR knock-out mice.

Results: Treatment with TGFβ (5 ng/ml) in HK2 cells resulted in an increase in the level of LC3 protein and autophagy related genes, along with an increase in fibrosis markers. Activation of FXR by GW4064 (200nM) in TGFβ-induced HK2 cells further increases expression levels of LC3 and autophagy related genes, whereas fibrosis markers were decreased. Also, autophagic flux was further increased on co-treatment with GW4064 and TGFβ in HK2 cells. Autophagy related genes has no GW4064 effects on down-regulation of FXR by siRNA in HK2 cells.

Conclusions: These data reveal a functional role of FXR for kidney autophagy regulator in TGFβ-induced HK2 cells and suggest that FXR may play an important role in the suppression of renal fibrosis through kidney autophagy.