KSN 2017 Abstract

KSN-17-O010

PGC-1α protects TGF-β induced fibrosis by suppressing TGFβRI expression affected to Smad2/3 activation

Hoon-in CHOI, Jung-sun PARK, Dong-hyun KIM, In-jin KIM, Eun hui BAE, Seong kwon MA, *Soo wan KIM

Department of Internal Medicine, Department of Internal Medicine, Chonnam National University Medical School, Gwangju, Republic of Korea, Korea,South

Objectives : Renal fibrosis results from aberrant accumulation of extracellular matrix mainly driven by transforming growth factor-β (TGF-β). This process is initiated by binding of active TGF-β1 to TGF β type I and type II receptor (TGFβRI and II) complex, which is transduced to intracellular signals for pro-fibrotic gene expression through Smad2/3 activation. Peroxisome proliferator-activated receptor gamma co-activator 1 alpha (PGC-1α) is a key metabolic regulator that stimulates mitochondrial biogenesis, and may play a role in oxidative stress and inflammation. However, the physiological effects of PGC-1α in renal fibrosis have not been fully characterized and the underlying mechanisms remain poorly understood. We investigated whether PGC-1α may regulate TGF-β/Smad signal pathways in the pathogenesis of renal fibrosis.

Methods : As in vivo and in vitro model of renal fibrosis, Left kidneys of C57BL/6J mice were subjected to unilateral ureteral obstruction (UUO) for 7 or 14 days. Human proximal tubule (HK-2) cells were stable transduced with human PGC-1α expression vector (PGC-1α) or empty vector (Mock) containing zeocin selective marker and were treated with TGF-β for the indicated time.The changes of pro-fibrotic marker proteins and signal molecules in TGF-β-treated Mock and PGC-1α stable cells were assessed by western blotting and immunofluorescence.

Results : The level of PGC-1α was diminished throughout the course of ureter obstruction and conversely associated with increased levels of fibrotic cytokine and fibrotic markers, such as TGF-β, fibronectin, vimentin, and alpha-smooth muscle actin (α-SMA). Consistent with in vivo data, the level of PGC-1α were reduced in TGF-β treated HK-2 cells. PGC-1α stable cells attenuated the TGF-β induced upregulation of fibrotic markers (fibronectin, vimentin, and α-SMA) and downregulation of epithelial marker (E-cadherin), compared to Mock cells. Overexpression of PGC-1α significantly suppressed TGFβRI expression, and subsequently phosphorylation of Smad2/3 was reduced.

Conclusions : PGC-1α regulates canonical TGF-β/Smad signal pathway by

targeting TGFβRI expression, resulting in anti-fibrotic effect.

Keywords : PGC-1α, TGF-β/Smad pathway, fibrosis