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# PGC-1alpha protects TGF-β induced fibrosis by suppressing let7c-mediated TGFβRI expression

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**Objectives:** TGF-β (transforming growth factor-β) is known as a central mediator in renal fibrosis. Recently, TGF-β decreases a microRNA let-7c and this is associated with increased expression of let-7c targets, including TGFβ receptor type 1 (TGFβRI). The peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α) is a master player that regulates mitochondrial biogenesis and the antioxidant response. However, the physiological effects of PGC-1α in renal fibrosis have not been fully characterized and the underlying mechanisms remain poorly understood.

**Methods:** Human proximal tubule (HK-2) cells were stable transduced with human PGC-1α expression vector (PGC-1α$^{O/E}$) or empty vector (PGC-1α$^{Mock}$) containing zeocin selective marker and were treated with TGF-β for the indicated time. The change of gene expression (fibrotic markers, TGFβRI, TGFβRII, and let-7c) and activation of signal molecules (phosphor form of Smad2/3) in TGF-β treated both PGC-1α$^{Mock}$ and PGC-1α$^{O/E}$ cells were compared by western blotting, real-time PCR, immunofluorescence.

**Results:** Consistent with down-regulation of PGC-1α in fibrotic progression of UUO-induced kidney, the mRNA level and protein level of PGC-1α also were reduced in TGF-β treated HK-2 cells. Stable expression of hPGC-1α in HK-2 cells (PGC-1α$^{O/E}$) attenuated the TGF-β induced upregulation of fibrotic markers (fibronectin, vimentin, and α-SMA) and downregulation of epithelial marker (E-cadherin), compared to PGC-1α$^{Mock}$. Overexpression of PGC-1α significantly was delayed phosphorylation of Smad2/3. PGC-1α$^{O/E}$ cells were specifically down-regulated in mRNA and protein level of TGFβRI, but not TGFβRII. We identified that let-7c was regulated by PGC-1α-specific manner and anti-fibrotic effects in PGC-1α$^{O/E}$ cells was resulted by down-regulation of TGFβRI mediated by upregulation of let-7c.

**Conclusions:** PGC-1α regulates canonical TGF-β/Smad2/3 signal pathway by targeting let-7-mediated TGFβRI expression, resulting in anti-fibrotic effect.