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Tamoxifen attenuates renal fibrosis through Src kinase in obstructive nephropathy in rats

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Objectives: Tubulointerstitial fibrosis is the final pathway of chronic progressive kidney diseases. Tamoxifen, a selective estrogen receptor (ER) modulator, attenuates renal fibrosis by regulating transforming growth factor (TGF)-β/Smad signaling in a mouse model. Src kinase and phosphoinositide 3-kinase (PI3K)/Akt pathways play critical roles in the pathogenesis of renal fibrosis. However, non-canonical TGF-β1/Smad signaling in renal fibrosis after treatment with tamoxifen remain unclear.

Methods: Renal fibrosis was induced by 14 days of unilateral ureteral obstruction (UUO) in male Sprague-Dawley rats. Tamoxifen (10 mg/kg) was given by oral gavage after UUO. We also treated human proximal tubular epithelial (HK-2) cells with tamoxifen in the presence or absence of TGF-β1 (2 ng/mL). The ER-α antagonist, ICI (5 μM), and ER-α receptor siRNA were used to examine the effects of tamoxifen treatment on ER-α-mediated TGF-β1-stimulated renal fibrosis.

Results: Tamoxifen treatment ameliorated UUO-induced renal fibrosis as shown by decreased expression of α-smooth muscle actin (SMA), fibronectin, and connective tissue growth factor (CTGF). Phosphorylation of Src (Tyr 416), PI3K/Akt, and mammalian target of rapamycin (mTOR)/p70S6K proteins was also significantly decreased in tamoxifen- compared to vehicle-treated UUO kidneys. Tamoxifen dose-dependently suppressed TGF-β1-induced expression of α-SMA and CTGF proteins, and phosphorylation of Src, PI3K/Akt, and mTOR/p70S6K in HK-2 cells *in vitro*. These antifibrotic effects were blunted by treatment with ICI and silencing ER-α with siRNA. Moreover, potent reduced renal fibrosis and inhibition of PI3K/Akt and mTOR/p70S6K were observed in HK-2 cells co-treated with PP1 (an Src kinase inhibitor) and tamoxifen.

Conclusions: Tamoxifen-induced antifibrotic effects are associated with the suppression of Src kinase via ER-α, followed by inhibition of phosphorylation of PI3K/Akt and mTOR/p70S6K signaling pathways.