S-D11

Tamoxifen Decreases Tubulointerstitial Fibrosis by Modulation of ERα-mediated TGFβ/Smad Signaling Pathway

Dal Kim, Ae Sin Lee, Yu Jin Jung, Sik Lee, Sung Kwang Park
Won Kim, Kyung Pyo Kang

Department of Internal Medicine, Research Institute of Clinical Medicine and
Diabetes Research Center, Chonbuk National University Medical School

Introduction: Renal fibrosis is the common pathway of all renal injury that ultimately leads to chronic and end-stage renal disease. One of the hallmarks of progressive and chronic kidney disease is the induction of tubulointerstitial fibrosis. TGFβ1 has been shown to play a critical role in the pathogenesis of tubulointerstitial fibrosis. Tamoxifen, known as selective estrogen receptor modulator (SERM), has been used antiestrogen for the prevention and treatment of the breast cancer as well as beneficial effects on bone after menopause women as action of ER agonist. Recently, there are some studies that tamoxifen inhibits fibroblast proliferation in human dermal fibroblast, collagen synthesis in mesangial cells, suppresses TGF-β and plasminogen activator inhibitor (PAI)-1 in hypertensive nephrosclerosis model. Therefore, we investigated the effect of tamoxifen on tubulointerstitial fibrosis and their mechanisms in UUO-induced renal tubulointerstitial fibrosis.

Method: Renal fibrosis was induced by unilateral ureteral obstruction (UUO) in the six-week-old C57BL/6 mice for 14 days. Tamoxifen (50 mg/kg) was treated by oral for 7 days before induction of renal fibrosis. Renal fibrosis and inflammation were determined by PAS, Masson trichrome stain, F4/80 and intercellular adhesion molecule-1 (ICAM-1) immunostaing. For determining of regulation of α-smooth muscle actin (α-SMA) expression by tamoxifen, NRK-49F cell was used.

Results: The PAS and MTS staining data show that Tamoxifen decreases renal tubular injury and fibrosis induced by UUO. Tamoxifen also decreases UUO induced a-SMA and FSP-1 immunofluorescence staining. Especially, we confirmed Tamoxifen ameliorates a-SMA, collagen type 1, vimentin, and fibronectin by immunoblotting. In addition, there are significantly decreases in macrophage infiltration at F4/80 and ERHR3 staining. Eventually, Tamoxifen decreases TGF β1 expression in tissue by ELISA. Western blot data show that pSmad2 and pSmad3 were decreased,however Smad7 expression was increased. As well, in NRK-49F cell, we confirmed Tamoxifen reduces TGFβ-1 induced aSMA and pSmad2 expression. But also, this decrease was reversed when treating antagonist ICI 182,780 with tamoxifen together.

Conclusion: Our finding suggested that tamoxifen has a beneficial effect on tubulointerstitial fibrosis in UUO model through modulation of ER-mediated TGF-β signaling.

Key Words: 만성신질환, Tamoxifen, 에스트로겐 수용체
UUO, Tamoxifen, Estrogen receptor-alpha