S-B7

Heat shock protein 90 억제제에 의한 신장의 항섬유화 효과

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Heat Shock Protein 90 Inhibitor Attenuates Renal Fibrosis

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The accumulation of extracellular matrix proteins and epithelial to mesenchymal transition (EMT) of renal tubular cells are common features of fibrotic kidney diseases. Accumulating evidence suggests that TGF-β1 promote the development of renal fibrosis. Heat shock protein 90 (Hsp 90) inhibitors have been shown to repress TGF-β1 signaling, but whether they inhibit renal fibrosis is unknown. The purpose of this study is to determine therapeutic efficacy of Hsp90 inhibitor on renal fibrosis. Unilateral ureteral obstruction (UUO) was induced in CD1 mice. Kidneys were analyzed at day 14. For in vitro studies, human proximal tubular epithelial cells (HK2) were stimulated with TGF-β1. In UUO kidneys and TGF-β1 treated HK2 cells, we found that 17-allylamino-17-demethoxygeldanamycin (17AAG), an Hsp 90 inhibitor, decreased expression of fibronectin, collagen I, and α-smooth muscle actin, and largely restored the expression of E-cadherin. In cultured HK2 cells, 17AAG inhibited TGF-β1-mediated phosphorylation of Smad2, Akt, glycogen synthase kinase-3β, and ERK. Inhibition of Hsp 90 also blocked TGF-β1-mediated induction of snail. This 17AAG-induced reduction was almost completely restored by treatment with proteasome inhibitor MG132. Interaction of TGF-β receptor type II (TβRII) with Hsp 90 was decreased by inhibition of Hsp 90. Immunohistochemical staining of TβRII showed increased TβRII expression in UUO kidneys as compared to control. 17AAG decreased TβRII protein expression in a dose-dependent manner. These findings suggest that 17AAG might decrease Smad and non-Smad signaling via a mechanism dependent on proteasome-mediated degradation of TβRII. In summary, Hsp 90 inhibitor may have therapeutic potential for TGF-β1-related fibrotic kidney diseases.

Key Words: Hsp 90 억제제, TGF-β1, 신장섬유화
Hsp 90 inhibitor, TGF-β1, Renal fibrosis