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Hsp90 억제제가 신장섬유화에 미치는 영향

순천향대학교 내과학교실[1], 현암신장연구소[2]

노현진[1] · 김현주[2] · 유미라[2] · 권순효[1] · 전진석[1] · 한동철[1]

Heat Shock Protein 90 Inhibitor Attenuates Renal Fibrosis

Hyunjin Noh[1], Hyun Joo Kim[2], Mi Ra Yu[2], Soon Hyo Kwon[1], Jin Seok Jeon[1], Dong Cheol Han[1]

Department of Internal Medicine[1], Hyonam Kidney Laboratory[2]

The accumulation of extracellular matrix proteins in the interstitial area is the final common feature of chronic kidney diseases. Accumulating evidence suggests that TGF-β1 promotes the development of renal fibrosis. Heat shock protein (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. In TGF-β1 treated HK2 cells and unilateral ureteral obstruction (UUO) kidneys, we found that 17-allylamino-17-demethoxygeldanamycin (17AAG), an Hsp90 inhibitor, decreased the expression of α-smooth muscle actin, fibronectin, and collagen I and largely restored the expression of E-cadherin. 17AAG inhibited TGF-β1-mediated phosphorylation of Smad2, Akt, glycogen synthase kinase-3, and ERK in HK2 cells. Inhibition of Hsp90 also blocked TGF-β1-mediated induction of snail1. This 17AAG-induced reduction was completely restored by simultaneous treatment with proteasome inhibitor MG132. Furthermore, 17AAG blocked the interaction between Hsp90 and TβRII and promoted ubiquitination of TβRII, leading to the decreased availability of TβRII. Smurf2-specific siRNA reversed the ability of 17AAG to inhibit TGF-β signaling. The effect of 17AAG on TβRII expression and renal fibrosis was confirmed in UUO kidneys. These findings suggest that Hsp90 inhibitor prevents the development of renal fibrosis via a mechanism dependent on Smurf2-mediated degradation of TβRII.

Key Words: Hsp90 억제제, 신장, 섬유화, 전환성장인자 β
Hsp90 inhibitor, Renal fibrosis, TGFβ