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알부민에 의해 유발되는 epithelial-mesenchymal transition과 ER stress에서의 공통 신호 전달 경로: imatinib mesylate의 효과

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Albumin-induced Epithelial-mesenchymal Transition and ER Stress are Regulated Through a Common ROS-c-Src Kinase-mTOR Pathway: Effect of Imatinib Mesylate

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Epithelial-mesenchymal transition (EMT) and endoplasmic reticulum (ER) stress induced by urinary protein, particularly albumin, play an important role in tubulointerstitial injury. However, signaling pathways regulating both albumin-induced EMT and ER stress are not precisely known. We postulated that reactive oxygen species (ROS), c-Src kinase and mTOR would act as upstream signaling molecules. We further examined the effect of imatinib mesylate on these processes. All experiments were performed using HK-2 cells, a human proximal tubular cell line. Protein and mRNA expression were measured by Western blot analysis and real time PCR, respectively. Exposure of tubular cells to albumin (5 mg/ml) for up to 5 days induced EMT in a time dependent manner, as shown by conversion to the spindle-like morphology, loss of E-cadherin protein, and up-regulation of α-smooth muscle actin mRNA and protein. Albumin also induced ER stress as evidenced by phosphorylation of eIF2α and increased expression of GRP78 mRNA and protein. Albumin induced ROS, c-Src kinase and mTOR as well. Anti-oxidants, c-Src kinase inhibitor (PP2) and mTOR inhibitor (rapamycin) suppressed the albumin-induced EMT and ER stress. Anti-oxidants and PP2 inhibited the albumin-induced c-Src kinase and mTOR, respectively. Imatinib suppressed the albumin-induced EMT and ER stress via inhibition of ROS and c-Src kinase. Imatinib also inhibited the albumin-induced mRNA expression of MCP-1, VCAM-1, TGF-β1, collagen I (α1). In conclusion, ROS-c-Src kinase-mTOR pathway played a central role in the signaling pathway that linked albumin to EMT and ER stress. Imatinib might be beneficial in attenuating the albumin-induced tubular injury.

Key Words: 알부민, c-Src, imatinib, mTOR, ROS
Albumin, c-Src, Imatinib, mTOR, ROS