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소포체 스트레스 전처리에 의한 TGF-β로 유도되는 신장상피세포의 상피-중간엽 세포이행의 억제효과

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Preconditioning of Endoplasmic Reticulum Stress Attenuated Epithelial-to-Mesenchymal Transition of Renal Tubular Cells induced by TGF-β

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Epithelial-to-mesenchymal transition (EMT) of renal tubular cell is known to be an early and a key process of renal fibrosis, however there are still controversies regarding the mechanism of EMT. Endoplasmic reticulum (ER) stress is a cellular stress pathway induced by the accumulation of unfolded proteins in the ER which is initially a defense mechanism of cells against various stressful environment to adaptation, however cell apoptosis develops with prolonged activation of ER stress. ER stress is reported to play a role in animal models of ischemia/reperfusion injury with a protective role of ER stress preconditioning in renal function. However, there is still limited knowledge on the pathophysiologic role of ER stress in progression of various kidney disease with few data of in-vitro experiment using renal tubular cells. To investigate the role of ER stress on renal disease progression, we examined the effect of ER stress preconditioning on EMT induced by transforming growth factor-β (TGF-β), a key cytokine of renal damage. Optimal preconditioning concentration of tunicamycin (TM) or thapsigargin (TG) and treatment duration that expressed 2 ER stress chaperones (GRP78/94 and eIF-1α) without an evidence of cell apoptosis were determined. To induce ER stress preconditioning, HK-2 cells were treated with 0.01 □g/mL of TM or 0.01 □M of TG for 4 hours, followed by a removal of TM or TG. EMT was evaluated with comparing the expression of epithelial cell marker, E-cadherin and mesenchymal cell marker, α-SMA. Exposure of HK-2 cells to TGF-β (10 ng/mL) for 24 to 72 hours resulted in a changes in cell morphology from cobble stone appearance to elongated, fibroblastoid morphology. TGF-β also decreased E-cadherin expression with an increase in α-SMA from 48 hours of stimulation. Preconditioning with TM or TG protected HK-2 cells from TGF-β-induced changes in cell morphology at 48 hours of stimulation, and also reversed the changes in the expression of E-cadherin and α-SMA by TGF-β. TGF-β-induced cell senescence assessed by senescence-associated (SA) β-gal staining was also ameliorated by pre-treatment with TM or TG. In conclusion, our finding suggests ER stress preconditioning protects renal tubular cells from phenotypic transformation, which can be a potential therapeutic target to prevent the progression of chronic kidney disease. Further studies are necessary to verify the role of ER stress preconditioning in animal model of chronic kidney disease.

Key Words : 소포체 스트레스, 상피중간엽 세포 이행, 만성신질환
ER stress, EMT, Chronic Kidney Disease