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Beneficial Effect of Glucocorticoid on Phenotypic Transformation of Human Peritoneal Mesothelial Cells and Fibroblasts

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Although the exact mechanisms of peritoneal fibrosis during PD still remain unclear, epithelial-to-mesenchymal transition (EMT) of peritoneum has been regarded as a key process of peritoneal fibrosis. It has been demonstrated that glucocorticoid restores the deterioration of water transport in the peritoneum and protects against the encapsulating peritoneal sclerosis in animal model of PD. On the other hand, glucocorticoid was known to activate TGF-β and other profibrotic proteins in hepatocytes. In this study, we investigated the effects of glucocorticoid on TGF-β-induced EMT in HPMCs and mesenchymal-to-epithelial transition (MET) of peritoneal fibroblast.

EMT or MET was evaluated by morphological changes of peritoneal cells and comparing the expression of epithelial cell marker, E-cadherin and mesenchymal cell marker, α-smooth muscle actin (α-SMA) after stimulation of TGF-β with or without pretreatment of dexamethasone (1, 5, 10 μM) or hydrocortisone (1, 5, 10 μM) by Western blotting. To examine the effect of steroid on TGF-β-induced cell signaling pathway, phosphorylation of ERK1/2 and p38 MAPK were also assessed.

TGF-β (>1 ng/mL) induced a morphological transformation from cuboidal and cobble stone appearance to spindle shaped scattered fibroblast-like cells at 48hrs, which was inhibited by pre-treatment of dexamethasone (5 μM) and hydrocortisone (10 μM). TGF-β down-regulated E-cadherin and up-regulated α-SMA expression at 48 hours, which were significantly attenuated by pre-treatment with dexamethasone or hydrocortisone. Furthermore, TGF-β-induced changes in the expression of E-cadherin and α-SMA were reversible with a removal of TGF-β after 48 hours of stimulation and subsequent exposure to dexamethasone or hydrocortisone. TGF-β significantly increased phosphorylation ERK1/2 and p38 MAPK in HPMCs from 5 minutes of stimulation, which was also blocked by dexamethasone or hydrocortisone. Interestingly, dexamethasone increased E-cadherine expression and decreased α-SMA expression in human peritoneal fibroblasts. Glucocorticoid inhibited TGF-β-induced EMT in HPMCs via ERK1/2 and p38 MAPKinase-dependent pathway with an induction of MET of peritoneal fibroblast. These results suggest glucocorticoid may be one of the possible therapeutic strategies to prevent peritoneal fibrosis in PD patients. Further studies are necessary to understand the exact mechanism of beneficial effect of glucocorticoid on peritoneal damage.

Key Words : 글루코 코르티코이드, 복막투석, 상피중간엽 세포이행
Glucocorticoid, peritoneal dialysis, EMT