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TGF-β에 의한 상피-중간엽전이 : MAPK & Smad 신호전달체계의 역할

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TGF-β-induced Epithelial-mesenchymal Transition (EMT) of Human Peritoneal Mesothelial Cell (HPMC) : Role of MAPK & Smad Signaling Pathway

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Purpose : Recent studies have identified the process of EMT as a potential key mechanism of peritoneal fibrosis. TGF-β is known to be a main inducer of organ fibrosis. However, intracellular mechanism of TGF-β-induced EMT in peritoneal fibrosis has not been thoroughly studied. Smad and the mitogen-activated protein kinase (MAPKinase) pathways have been known to be associated with TGF-ß signaling. In this study, we performed an in-vitro study in cultured HPMCs to identify intracellular signaling pathway of TGF-β-induced EMT and to test its therapeutic potential as anti-fibrotic treatment in peritoneal dialysis.

Methods : EMT was evaluated by comparing the expression of E-cadherin and α-smooth muscle actin (α-SMA) in HPMCs exposed to TGF-β (0.01, 0.1, 1, 10 ng/mL) for 48 hours. The activation of Erk and p38 MAPK was assessed by western blotting of TGF-β-treated cells. Effect of Erk or p38 MPAKinase on TGF-β-induced EMT was examined in cells treated with MAPK inhibitors, PD98059 (10 mM) or SB203580 (10 mM). To investigate the role of smad3 pathway on TGF-β-induced EMT, cells were transfected with samd3-siRNA (200 pmole) or control-siRNA (100 pmole) using lipofectamine 2000.

Results : TGF-β induced EMT of HPMCs in a dose-dependent manner, and was reversible by the removal of TGF-β stimulation. TGF-β stimulation increased the phosphorylation of Erk, whereas no effect on p38 MAPkinase activation in HPMCs. Consistent with these findings, Erk inhibitor PD98059, but not p38 inhibitor SB203580 blocked TGF-β-induced EMT. In addition, transfection of HPMCs with Smad3-siRNA ameliorated TGF-β-induced EMT.

Conclusion : Activation of Erk & Smad signaling pathway play a key role in TGF-β-induced EMT of HPMCs. Further understanding of the mechanisms of TGF-β-induced EMT may offer therapeutic targets preventing peritoneal membrane damage.