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Effect of Plasminogen activator inhibitor-1 (PAI-1) on Phenotype Transition of Human Peritoneal Mesothelial Cells (MCs)

Dal-Ah Kim, Hyun-Jung Kang, Yerim Her, Duk-Hee Kang
Department of Internal Medicine, Ewha Womans University Medical Center, Korea, Republic of

Objectives: The epithelial-to-mesenchymal transition (EMT) of MCs is an early mechanism of peritoneal dysfunction in peritoneal dialysis (PD). Plasminogen activator inhibitor-1 (PAI-1) was initially known as an inhibitor of fibrinolysis by hindering the proteolytic activity of tissue type plasminogen activator and urokinase-type plasminogen activator, and recently reported to regulate EMT of cancer cells. However, there are no studies on the association of PAI-1 and peritoneal EMT.

Methods: EMT was evaluated by morphological changes of MCs and the expressions of E-cadherin and α-smooth muscle actin (α-SMA) after TGFβ (1 ng/mL) stimulation by real time PCR, Western blotting (WB) and immunostaining. Effect of gene silencing of PAI-1 on EMT was examined using siRNA. E-cadherin promoter activity was confirmed by luciferase assay. Activation of Smad2/3, Erk1/2 MAPK, AKT phosphorylation, snail expression, nuclear translocation of snail was also assessed. The expressions of MMP2 and MMP9 were evaluated by real time PCR and WB. Effect of PAI-1 inhibitor (Tiplaxtinin; PAI-039, 20 uM) on TGFβ-induced EMT was also examined.

Results: TGFβ stimulation resulted in an increased expression of PAI-1 mRNA and protein in MC. Both PAI-1 gene silencing and Tiplaxtinin ameliorated TGFβ-induced changes in cell morphology and the expression of E-cadherin, α-SMA, and fibronectin. TGFβ-induced decrease in E-cadherin promoter activity and nuclear translocation of snail were also alleviated by siPAI-1. PAI-1 gene silencing ameliorated TGFβ-induced activation of smad2/3 (30 min), Erk1/2 MAPK (1 hour), and AKT (8 hour) pathways. In addition, siPAI-1 ameliorated TGFβ-induced MMP2 expression (30 min), but did not affect MMP9 expression in MCs.

Conclusions: PAI-1 play a role in TGFβ-induced EMT of peritoneal MCs, and modulation of PAI-1 expression/activity in MCs could be a novel strategy to prevent peritoneal fibrosis in PD patients.