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Blocking Plasminogen activator inhibitor-1 (PAI-1) ameliorates the functional and structural deterioration of peritoneum in animal model of peritoneal dialysis (PD)

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Objectives: Long-term exposure to PD solution leads to progressive peritoneal fibrosis which is initiated from phenotype transition of peritoneal mesothelial cells (MC) such as epithelial-to-mesenchymal transition (EMT). Plasminogen activator inhibitor-1 (PAI-1) is a well-known downstream pathway TGFβ signaling and recently reported to regulate EMT of cancer cells. However, there are no studies on the role of PAI-1 in peritoneal EMT and fibrosis.

Methods: PD mouse model (C57BL/6) was established by daily infusion of 4.25% glucose-based dialysate (PDS; 100mL/kg/day) for 4 weeks via intraperitoneal catheter with or without oral administration of PAI-1 inhibitor (Tiplaxtinin, 5mg/kg/day). In 4 weeks of PD, dialysate/plasma ratio of creatinine (D/P_{Cr}) and the 2-hour-dialysate/initial dialysate ratio of glucose (D/D_0glu) were measured. For histologic analysis, the abdominal wall was stained with hematoxylin and eosin for evaluation of peritoneal thickness. For in-vitro experiment, EMT was evaluated by morphological changes of MCs and the expression of E-cadherin and α-SMA by real-time PCR, WB and ICC. E-cadherin promoter activity, activation of Smad2/3, Erk1/2, AKT, nuclear translocation of snail and MMP expression were assessed. ROS generation was assessed by DCF-DA, MitoSox staining, and NOX mRNA expression.

Results: In mouse PD model, Tiplaxtinin ameliorated the changes in D/D_0glu and D/P_{Cr} with a decrease in peritoneal thickness. TGFβ (1 ng/ml) stimulation resulted in an increased expression of PAI-1 mRNA and protein in MCs. TGFβ-induced EMT was ameliorated by siPAI-1 or Tiplaxtinin (20 μM). TGFβ-induced nuclear translocation of snail and decrease of E-cadherin promoter activity were also alleviated by siPAI-1. siPAI-1 inhibited TGFβ-induced activation of Smad2/3, Erk1/2, AKT and MMP2 expression. Tiplaxtinin alleviated NOX- and mitochondria-mediated ROS production.

Conclusions: PAI-1 plays a role in peritoneal EMT and fibrosis, which could be a novel strategy to preserve functional and structural integrity of peritoneal membrane in PD patients.