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Periostin-binding DNA aptamer ameliorates peritoneal dialysis-induced peritoneal fibrosis

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Background: Peritoneal fibrosis (PF) is a major complication, leading to ultrafiltration failure in patients on peritoneal dialysis (PD). In PD-related PF, the protein expressions of various extracellular matrix including periostin are known to be increased via the transforming growth factor-β1 (TGF-β1) pathway. This study was undertaken to evaluate the impact of periostin inhibition by novel aptamer-based inhibitor on TGF-β1-induced epithelial-mesenchymal transition (EMT) in cultured human peritoneal mesothelial cells (HPMCs) and in an animal model of PD.

Methods: *In vitro*, primary HPMCs were exposed to TGF-β1 (2 ng/ml) to induce EMT and fibrosis with or without periostin siRNA (100 nM) or periostin-binding DNA aptamer (200 nmol/l). *In vivo*, PD catheters were inserted into 48 C57BL/6 mice, and saline (C group, N=24) or 4.25% PD solution (PD group, N=24) was infused for 4 weeks. Twelve mice from each group were treated with periostin-binding DNA aptamer (500 μg/kg/d) (PA). mRNA and protein expressions of periostin, fibronectin, α-smooth muscle actin (α-SMA), snail, and E-cadherin in HPMCs and mouse peritoneum were evaluated by quantitative real-time polymerase chain reaction and western blot analysis, respectively. PF was also assessed by Masson's trichrome (MT) staining.

Results: *In vitro*, TGF-β1 treatment significantly up-regulated periostin, fibronectin, α-SMA, and snail expressions, while E-cadherin expression was significantly decreased by TGF-β1 in cultured HPMCs ($P < 0.01$). Not only periostin siRNA but also periostin-binding DNA aptamer significantly attenuated TGF-β1-induced periostin, fibronectin, α-SMA, and snail expressions and significantly restored E-cadherin expression in HPMCs ($P < 0.05$). *In vivo*, the expressions of periostin, fibronectin, α-SMA, and snail were significantly increased, whereas E-cadherin expression was significantly decreased in the peritoneum of PD mice ($P < 0.05$). The thickness of the submesothelial layer and the intensity of MT staining in the peritoneum were significantly higher in PD mice compared to C mice ($P < 0.05$). These changes in the PD group were significantly abrogated by PA treatment ($P < 0.05$).

Conclusion: These findings suggest that PA can be a potential therapeutic strategy for PF in PD patients.

Keywords: Aptamer, Epithelial-mesenchymal transition, Periostin, Peritoneal dialysis, Peritoneal fibrosis, Transforming growth factor-β1