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**The Effect of Protein Transduction Domain Recombinant Bone Morphogenetic Protein-7 on Epithelial-Mesenchymal Transition in Peritoneal Mesothelial Cells**

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**Background:** Previous studies have demonstrated that peritoneal fibrosis (PF) via epithelial-mesenchymal transition (EMT) is a serious complication in long-term peritoneal dialysis (PD) patients. In addition, transforming growth factor-β1 (TGF-β1) is known to play an important role in the process of EMT and bone morphogenetic protein-7 (BMP-7) is widely investigated as the counter-regulator of TGF-β1 to maintain the balance of their biological activities. Protein transduction domain (PTD), composing of 10~16 basic amino acid residues, has ability delivering macromolecule across the plasma membrane without receptor, allowing proteins to accumulate within the cell. In this study, we investigated the effect of PTD-mediated BMP-7 (tissue-regeneration polypeptide 2, TRP2) on TGF-β1-induced EMT in cultured human peritoneal mesothelial cells (HPMCs). In addition, we investigated how to deliver the drugs to peritoneum in vivo models.

**Methods:** In vitro, HPMCs were cultured in M199 media containing 5.6 mM glucose (normal glucose, NG), NG + TGF-β1 (2 ng/ml) with or without TRP2 (100 ng/ml). After 72 hours, cells were harvested. In vivo, PD rat-O-port inserted into 11 Sprague-Dawley rats, and saline (control group, n=3), 4.25 % PD solution (PD group, n=3) or 4.25 % PD solution + TRP2 (PD + TRP2 group, n=5) were infused for 4 weeks. After 4 weeks, rats were sacrificed and the peritoneal tissues were removed. E-cadherin, ZO-1, α-smooth muscle actin (α-SMA), snail, vimentin, type I collagen, and fibronectin protein expression in HPMCs and the peritoneum were estimated by western blot analysis, and fibronectin expression was evaluated by immunohistochemistry staining. PF was assessed by Masson's trichrome (MT) staining.

**Results:** In vitro, protein expression of E-cadherin and ZO-1 (epithelial marker) were significantly decreased, while α-SMA, snail, vimentin (mesenchymal marker), type I collagen and fibronectin were significantly increased in TGF-β1-stimulated HPMCs compared to control group, and these changes were significantly improved by TRP2 treatment. In vivo, peritoneal EMT and PF were significantly increased in PD rats compared to control rats. The thickness of mesothelial layer and the intensity of MT staining in the peritoneum of PD rats were also significantly higher compared to control rats. These changes of the peritoneum in PD rats were significantly ameliorated by the administration of TRP2.

**Conclusion:** This study suggests that TRP2 directly inhibits the process of TGF-β1-induced PF via peritoneal EMT in HPMCs. In addition, TRP2 mitigates PF in PD rats. The effect of PTD-mediated recombinant protein delivery system may be a potential therapeutic strategy for prevention of PF in PD patients.

**Keywords**: Epithelial-mesenchymal transition, Peritoneal mesothelial cell, Protein transduction domain recombinant bone morphogenetic protein-7, Tissue-regeneration polypeptide 2