

Wnt4의 발현 변화가 세뇨관 세포의 상피세포-간엽세포 이행 및 세뇨관-간질 섬유화 진행에 미치는 영향

연세대학교 의과대학 의생명과학부 Brain Korea 21 PLUS

김성훈, 남보영, 강혜영, 엄재은, 박지민, 오미연, 이미정, 박정탁, 한승혁, 유태현, 강신욱

The Role of Wnt4 in Epithelial-mesenchymal Transition and Tubulointerstitial Fibrosis

Seonghun Kim, Bo Young Nam, Hye-Young Kang, Jae Eun Um, Jimin Park, Meiyun Wu
Mi Jung Lee, Jung Tak Park, Seung Hyeok Han, Tae-Hyun Yoo, Shin-Wook Kang

Severance Biomedical Science Institute, Brain Korea 21 PLUS, Yonsei University College of Medicine

Background: Previous studies have demonstrated that Wnt/GSK-3/β-catenin pathway is related to renal fibrosis in various kidney diseases. However, although Wnt4 is abundantly expressed in renal tubule cells, the role of this specific Wnt subfamily in the pathogenesis of epithelial-mesenchymal transition (EMT) and tubulointerstitial fibrosis in kidney has not been fully explored yet. Therefore, the effect of Wnt4 on EMT and tubulointerstitial fibrosis in tumor growth factor-β1 (TGF-β1)-stimulated renal tubular cells and unilateral ureteral obstruction (UUO) mice models were examined.

Methods: In vitro, renal proximal tubular cells (NRK-52E) and immortalized mouse distal convoluted tubule cells (mDCT) were each cultured in DMEM media or DMEM/F12 media respectively. NRK-52E and mDCT cells were each treated with recombinant human TGF-β1 with or without Wnt4 siRNA transfection. The effect of recombinant Wnt4 protein treatment was also examined in those cells. Western blot analysis was performed to evaluate Wnt4, fibronectin, type I collagen, phospho-p38, and EMT-related proteins. In vivo, UUO was performed in C57BL/6 mice. Kidneys were harvested after 10 days of UUO. Immunohistochemistry for expression of Wnt4 was conducted with renal tissues.

Results: The mRNA and protein expression of Wnt4 were significantly higher in recombinant TGF-β1-stimulated NRK-52E and mDCT cells compared to control cells. Protein expressions of E-cadherin and Zo-1 were significantly decreased, while the expression levels of α-SMA, vimentin, and snail were significantly increased in those cells treated with recombinant TGF-β1 compared to controls. In addition, recombinant TGF-β1 treatment significantly upregulated fibronectin, type I collagen, and phospho-p38 protein expression levels in renal tubular cells. Transfection by Wnt4 siRNA in those cells significantly ameliorated TGF-β1 induced increments of fibronectin, type I collagen, and phospho-p38 proteins, although treatments of Wnt4 siRNA did not influence EMT related changes. In addition, recombinant Wnt4 in NRK-52E and mDCT cells also increased in protein expression of fibronectin and type I collagen. Immunohistochemical staining revealed a significant up-regulation of Wnt4 expression in UUO mice compared to control mice.

Conclusions: These findings suggest that Wnt4 may play a role in renal fibrosis. However, further investigations should be needed to clarify its role in EMT.

Key Words: Wnt4, 상피세포-간엽세포 이행, 섬유화

Wnt4, Epithelial-mesenchymal transition, Fibrosis