P-47

Activation of GPR40 Attenuates TNF-α-induced Apoptosis and EMT in Rat Proximal Tubular Cells by the Inhibition of AT1R/TACE

Seong Kwon Ma[1], In Jin Kim[1], Soo Yeon Joo[1], Hoon-In Choi[1], Jung Sun Park[1]
Eun Hui Bae[1], Jong Un Lee[2], Soo Wan Kim[1]

Departments of Internal Medicine[1] and Physiology[2], Chonnam National University Medical School

The pathophysiological roles of G-protein-coupled receptor 40 (GPR40) in the kidney disease have not yet been established. The present study investigated the changes of GPR40 expression in the obstructed kidney of mice with unilateral ureteral obstruction (UUO). We also investigated the effects of GPR40 activation on the apoptosis and epithelial-mesenchymal transition (EMT) induced by tumor necrosis factor (TNF)-α treatment in rat proximal tubular (NRK52E) cells. UUO was induced in C57BL/6J mice for 2 weeks. NRK52E cells were cultured with TNF-α in the absence or presence of GW9508, a selective GPR40 agonist. Following UUO, the protein expression of Bax was increased while that of Bcl-2 was decreased. The expression of transforming growth factor (TGF)-β1 and α-smooth muscle actin (SMA) was increased. In the mouse kidney, immunohistochemistry revealed higher immunoreactivity of GPR40 in the renal tubules of cortex and outer stripe of outer medulla. Double immunofluorescence staining showed that GPR40 immunoreactivity was colocalized with renal tubules expressing aquaporin (AQP)-1 and AQP2. Immunoreactivity of GPR40 was decreased in the ureteral obstructed kidney of mice. In NRK52E cells, the pretreatment with GW9508 attenuated the decreased cell viability by TNF-α treatment. TNF-α treatment increased the protein expression of Bax/Bcl-2, TGF-β1, connective tissue growth factor, α-SMA and fibronectin, which was ameliorated by GW9508 pretreatment. The protein expression of angiotensin II type 1 receptor (AT1R) and TNF-α converting enzyme (TACE) was increased following treatment with TNF-α. TNF-α treatment also activated the phosphorylation of Src/epidermal growth factor receptor/extracellular signal-regulated kinase. These changes were counteracted by pretreatment with GW9508. In conclusion, GPR40 is expressed in the proximal tubules and collecting ducts, and the expression of GPR40 is significantly decreased in the ureteral obstructed kidney of mice with UUO. In NRK52E cells, GPR40 activation attenuates TNF-α-induced apoptosis and EMT by the inhibition of AT1R and TACE.

Key Words: GPR40, AT1R, TNF-a