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Activation of GPR40 Attenuates Apoptosis and EMT Induced by TNF-α in Rat Proximal Tubular Cells

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G-protein-coupled receptor 40 (GPR40) plays diverse functions such as inhibition of apoptosis and inflammation. However, the pathophysiological roles of GPR40 in the pathogenesis of kidney diseases have not yet been identified. We have investigated the protein expression of GPR40 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. In the ureteral obstructed kidney of mice, the protein expression of GPR40 was decreased while that of Bax/Bcl-2, transforming growth factor (TGF)-β1 and α-smooth muscle actin (SMA) was increased. In NRK52E cells, the pretreatment of 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 (CTGF) and α-SMA, which was ameliorated by GW9508 pretreatment. TNF-α treatment activated the phosphorylation of Src/epidermal growth factor receptor (EGFR)/extracellular signal-regulated kinase (ERK), which was counteracted by the pretreatment of GW9508. In conclusion, the expression of GPR40 was decreased in the ureteral obstructed kidney of mice with UUO. In NRK52E cells, GPR40 activation attenuates the apoptosis and EMT induced by TNF-α through the inhibition of pro-apoptotic proteins, pro-fibrotic proteins, and Src/EGFR/ERK signaling pathway.

Key Words: GPR40, Apoptosis, EMT