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Ferroptosis is involved in renal tubular cell death in diabetic nephropathy

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Objectives : Tumor growth factor-β1 (TGF-β1)-induced cell death is known to contribute to the pathogenesis of diabetic nephropathy (DN), a major complication of diabetes. Ferroptosis, a new atypical form of cell death, is an iron-dependent cell death that is distinct from apoptosis, necroptosis, and autophagy, and results from lipid peroxide accumulation. In this process, two molecules, glutathione peroxidase 4 (GPX4) and glutamate/cystine antiporter (xCT), are surmised to be principally involved. Recently, ferroptosis has been reported to cause several kidney diseases, including acute kidney injury. However, the impact of ferroptosis on tubular cell death under diabetic conditions has never been elucidated.

Methods : In vitro, rat proximal tubular epithelial cells (NRK-52Es) were cultured in DMEM media containing 5.6 mM glucose (normal glucose, NG) or NG + TGF-β1 (10 ng/ml) with or without ferroptosis inhibitors (Ferrostatin-1 and Liproxstatin-1) or iron chelator (Deferoxamine) for 12 hours. In vivo, 12 C57BL/6 mice were intraperitoneally injected with saline (Control, C) (N=6) or STZ (50 mg/kg/d) for 5 consecutive days (Diabetes, DM) (N=6), and were sacrificed after 6 weeks. The protein expression of GPX4, xCT, hypoxia-inducible factor (HIF)-1α, heme oxygenase-1 (HO-1), and nuclear factor erythroid 2-related factor 2 (Nrf2) were determined in cultured tubular epithelial cells and the mouse kidneys by western blot analysis. Cell viability and lipid peroxidation (MDA) were also evaluated in cultured tubular cells.

Results : Compared to NG cells, the protein expression of xCT was significantly decreased, while HIF-1α, HO-1, and Nrf2 protein expression were significantly increased in TGF-β1-stimulated renal tubular epithelial cells. In contrast, GPX4 expression was not changed in renal tubular cells exposed to TGF-β1. Moreover, MDA levels were significantly increased along with significantly decreased cell viability in TGF-β1-stimulated cells. These changes in cultured tubular cells exposed to TGF-β1 were significantly ameliorated by ferroptosis

inhibitors or iron chelator treatment. A significant decrease in xCT protein expression was also observed in the kidney of DM mice compared to the C kidney.

Conclusions : These results suggest that ferroptosis is involved in renal tubular cell death under diabetic conditions and that ferroptosis inhibitor or iron chelator can be a promising therapeutic agent in patients with diabetic nephropathy.

Keywords : Ferroptosis, Cell death, Diabetic nephropathy, Oxidative stress