Conclusion: Calcitriol protects against renal tubular cell apoptosis by promoting M2 macrophage polarization in STZ-induced DN rats.

Autophagy-Lysosome Pathway in Renal Tubular Epithelial Cells is Disrupted by Advanced Glycation End Products in Diabetic Nephropathy

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Objective: Autophagy has been suggested to protect renal tubular epithelial cells (TECs) from injury during diabetic nephropathy (DN). However, the manner in which the autophagy-lysosome pathway is changed in this state remains unclear.

Methods: In this study of DN, we investigated the autophagic activity and lysosomal alteration in vivo and in vitro.

Results: We found that autophagic vacuoles and SQSTM1 positive proteins accumulated in TECs from patients with DN and also in HK-2 cells treated with advanced glycation end products (AGEs), the important factors that involved in the pathogenesis of DN. In HK-2 cells, exposure to AGEs caused a significant increase in autophagosomes, but a marked decrease in autolysosomes. Furthermore, the lysosomal turnover of LC3-II was not observed post AGEs treatment. Furthermore, lysosomal membrane permeabilization (LMP) was triggered by AGEs during the progression of DN, which likely resulted in a decrease in the enzymatic activity of cathepsin B (CB) and CL, the defective acidification of lysosomes, and suppressed the degradation of DQ-ovalbumin. Additionally, ubiquitinated proteins were co-localized with SQSTM1 positive puncta and accumulated in HK-2 cells after exposure to AGEs, indicating blocked degradation of SQSTM1 positive and ubiquitinated aggregates.

Conclusion: Taken together, LMP and lysosomal dysfunction are triggered by AGEs, which induce autophagic inactivation in TECs from patients with DN. Disruption of autophagy-lysosome pathway should be focused when studying the mechanisms underlying DN.

Cdk5 Regulates ERK1/2/PPARγ-mediated Renal Tubulointerstitial Fibrosis in Diabetic Nephropathy

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Objectives: Cyclin-dependent kinase 5 (Cdk5) has been documented in podocyte injuries in diabetic nephropathy (DN), however its role in renal tubular epithelial cells has not been elucidated. This study aims to investigate whether Cdk5 regulates tubulointerstitial fibrosis (TIF) via the extracellular signal-regulated kinase 1/2 (ERK1/2)/peroxisome proliferator-activated receptor gamma (PPARγ) pathway in DN.

Methods: Effects of activating or inhibiting Cdk5, ERK1/2 and PPARγ signaling on downstream gene expressions and epithelial-to-mesenchymal transition (EMT) were investigated using in vitro and in vivo approaches. Expressions of related molecules were validated in 86 archival DN patient renal biopsy samples and biological parameters were analyzed.

Results: In high glucose cultured normal rat kidney cells (NRK52E) cells, inhibition of Cdk5 kinase activity using roscovitine decreased the expression of mesenchymal markers and the ability of cells to migrate and invade via ERK1/2/PPARγ pathway (Figure 1). In diabetic rat kidneys, inhibition of Cdk5 kinase activity using roscovitine increased phosphorylation of ERK1/2 and PPARγ, leading to upregulation of E-cadherin but downregulation of vimentin and collagen IV and improved TIF. Blood urine nitrogen (BUN), serum creatinine and β2-microglobulin were decreased in DN patients’ renal biopsy samples (Figure 2), the expression level of Cdk5 and p35 were upregulated with increased phosphorylation of ERK1/2 and PPARγ in the late stage compared with early-stage DN. These changes were concomitant with decreased expression of E-cadherin but increased vimentin and collagen IV with deteriorated TIF and elevated BUN, serum creatinine and β2-microglobulin.