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Modulation of STAT3 ameliorates mitochondrial dysfunction induced by high glucose stimulation

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Objectives: Mitochondrial dysfunction is one of the mechanisms of progression of chronic kidney disease (CKD), and STAT3 is involved in the changes in mitochondrial function and survival. In this study, by targeting diabetic nephropathy, which is the most common cause of CKD, mitochondrial changes in high glucose-induced damage and the effect of STAT3 modulation on this were investigated.

Methods: Primary cultured tubular epithelial cells (TECs) and podocytes from human kidneys were used, the effects of STAT3 modulation were investigated in the H_2O_2-induced oxidative stress model, the rTGF-β induced fibrosis model, and the fibrosis model induced by glucose stimulation. Stattic, an irreversible STAT3 activation inhibitor, was used.

Results: In JC-1 assay, mitochondrial function damaged by H_2O_2-induced oxidative stress was restored after treatment with Stattic (1μM). Fibronectin, increased by rTGF-β treatment (2 ng/mL, 48 hours) in podocytes, decreased after treatment with Stattic, and the reaction was remarkable from 3 hours after treatment. TECs showed the same results, but the extent of reduction was less than that of podocytes. Next, high glucose stimulation (25, 50, and 100 mM, 48 hours) in podocytes increased fibronectin and TGF-β, and phosphorylated NF-κB. After glucose stimulation, decreased cell proliferation and increased IL-6 were restored and decreased in a dose-dependent manner by static treatment, respectively. Apoptosis was also dose-dependently decreased after Stattic treatment. STAT3 inhibition dose-dependently decreased cytochrome C mRNA expression; in contrast, the mRNA expression of PGC-1α was increased. All these results were more pronounced in podocytes than in TECs. In addition, an increase in pSTAT3 and a decrease in PGC-1α were demonstrated in kidney tissues of diabetic nephropathy patients.

Conclusions: Modulation of the expression of STAT3 in high glucose-induced kidney injury inhibits mitochondrial damage and improves renal function. Furthermore, STAT3 inhibition under high glucose conditions was more susceptible and effective to podocytes than TECs.

Figure 1. JC-1 assay

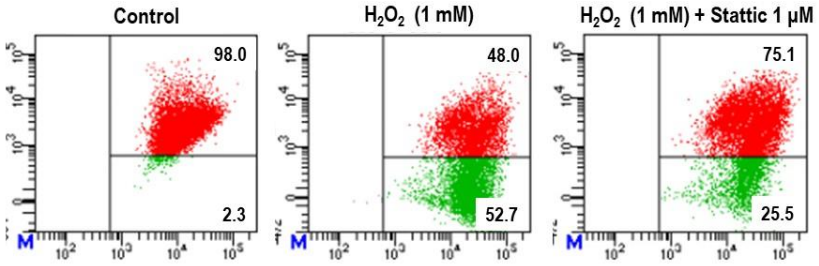

Figure 2. The effects of STAT3 modulation on mitochondrial function and cell survival