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Renoprotective Effect of KLF2 on Glomerular Endothelial Dysfunction in Hypertensive Nephropathy

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Objectives: Krupeel-like factor 2 (KLF2) is a transcription factor, which regulates endothelial cell metabolism. Endothelial dysfunction is associated with hypertensive nephropathy. Here, we present a role of KLF2 in hypertensive nephropathy.

Methods:

Human primary glomerular endothelial cells were harvested and cultured under pressure condition by a rotational force device. We evaluate the mRNA expression of α-smooth muscle actin (αSMA), KLF2 and KLF4 according various pressure. Also, cell apoptosis under pressure with/without KLF2 induction using simvastatin (1, 10uM) were accessed. To induce hypertensive nephropathy in rat (8 weeks old), 5/6 nephrectomy was done and kidney injury marker, blood pressure, KLF2 expression were evaluated. And KLF2 expression in hypertensive nephropathy patients' biopsied kidney tissue was evaluated.

Results:

The survival rate of human primary glomerular endothelial cells was maintained up to 4mmHg and decreased from above 4mmHg (cell survival: 4mmHg, 82.49% vs. 8mHg 71.01%). After the application of 4mmHg pressure for 48hr in cells, expression of KLF2 was decreased, while αSMA was increased and KLF4 was similar compared to control. Under hypertensive condition, KLF2 mRNA, cell viability were decreased, and Cyclin-dependent kinase inhibitor p21, apoptosis were increased. Simvastatin/KLF2 induction (10uM) significantly reduced p21 by half ($P<0.001$) and attenuated early apoptosis, necrosis compared to vehicle (early apoptosis: 3.2% to 0.6%, necrosis: 6.7% to 2.2%, all $P<0.05$). Also, cell viability was increased by simvastatin. 5/6 nephrectomy in rats resulted in increased blood pressure, decreased kidney function, as well as decreased KLF2 expression of glomerular endothelial cells. In addition, the expression of KLF2 in kidney of hypertensive nephropathy patients was lower than that of normal patients ($P<0.05$).

Conclusions: We found that KLF2 expression is decreased in glomerular endothelial cell hypertensive injury, whereas simvastatin reduces early apoptosis and necrosis, suggesting that early use of simvastatin/KLF2 induction could be a therapeutic option in hypertensive nephropathy.