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고포도당으로 자극된 사구체세포에서 PPAR-γ을 표적으로 세포비후와 소멸을 억제하는 klotho의 역할

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Klotho is a Target of PPAR-γ and Protective Against High Glucose-Induced Cellular Hypertrophy and Apoptosis in Glomerular Cells

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Background: Klotho is mainly expressed in the renal distal tubules and exerts coreceptor function for FGF23. It can also be released into the circulation by proteinase-induced cleavage or alternative splicing and acts like a hormone that can have anti-oxidative stress and anti-senescence effects. However, local effects of klotho on individual organs are largely unknown. In this study, we investigated whether klotho can exert a protective effect on high glucose (HG)-stimulated glomerular cells.

Methods: The protein expression of klotho and peroxisomal proliferator-activated receptor-gamma (PPAR-γ) was examined in HG-stimulated (30 mM) glomerular cells using Western-blot analysis in a time-dependent manner. To explore whether klotho expression is determined by PPAR-γ, we performed a chromatin-immunoprecipitation (ChiP) assay to clarify an interaction between the two proteins and evaluated the protein expression of klotho in glomerular cells treated with PPAR-γ agonist (pioglitazone, 50 μM) or antagonist (GW 9662, 20 μM). We also examined the expression of cyclin-dependent kinase inhibitors (p21Clip1 and p27Kip1) and apoptosis-related molecules (caspase-3, Bax, and Bcl-2) in HG-stimulated glomerular cells treated with recombinant klotho (rKL, 200 pM) or klotho SiRNA.

Results: The presence of klotho gene was confirmed using real-time PCR and immunofluorescence study in mouse mesangial cells and podocytes. The protein expression of PPAR-γ and klotho was increased up to 24 hours in HG-stimulated glomerular cells and decreased at 48 hours. The ChiP assay found PPAR-γ responsive element in the 5'-flanking region of the klotho gene and klotho expression was increased by PPAR-γ agonist and decreased by PPAR-γ antagonist. The expression of p21Clip1, p27Kip1, cleaved caspase-3, and the ratio of Bax/Bcl-2was significantly increased in HG-stimulated glomerular cells. rKL treatment significantly attenuated the increased expression of these proteins, whereas klotho siRNA further increased this expression.

Conclusion: This study demonstrated that klotho was a target of PPAR-γ in glomerular cells. We also showed that klotho contributed to the amelioration of cellular hypertrophy and apoptosis in HG-stimulated glomerular cells, suggesting that klotho may exert a protective role in glomerular cells under diabetic condition. Further studies using in vivo model are requiredto validate our findings.

Key Words: 클로토, 세포비후, 사구체세포
Klotho, cellular Hypertrophy, glomerular Cells