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만성 사이클로스포린 신병증에서 안지오텐신 II 수용체 길항제에 의한 노화방지 유전자, Klotho의 보호효과

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Angiotensin II Receptor Blockade Protects Klotho, an Anti-aging gene, in Chronic Cyclosporine Nephropathy

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Background : Klotho is a suppressor gene of multiple aging phenotypes. This study evaluated the role of renin-angiotensin system (RAS) in Klotho gene expression in experimental model of chronic cyclosporine (CsA) nephrotoxicity.

Methods : Three separate experiments were performed. First, mice were treated with losartan (LSRT, 100 mg/L), an angiotensin II receptor blocker, on a normal salt diet (NSD) or low salt diet (LSD). Second, mice were treated with CsA (30 mg/kg) for one or four weeks on a NSD or LSD. Third, mice on a NSD or LSD were treated with CsA and LSRT for 4 weeks. The expression of Klotho mRNA and protein, histopathology, and tissue expression of angiotensinogen were evaluated. The oxidative stress level was assessed by urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG) excretion as a mechanism of Klotho gene regulation.

Results : The LSD significantly decreased Klotho expression compared to the NSD ($p<0.05$), and the administration of LSRT reversed it. On the NSD, CsA treatment for 4 weeks markedly decreased Klotho expression compared to CsA treatment for 1 week ($p<0.05$). On the LSD, Klotho expression was significantly decreased by CsA treatment for 1 week ($p<0.05$) and almost completely suppressed by CsA treatment for 4 weeks. Concurrent administration of LSRT with CsA significantly increased Klotho expression, improved tubulointerstitial fibrosis, decreased tissue angiotensinogen expression and decreased urinary 8-OHdG level compared to the CsA group ($p<0.05$). There was a negative correlation between Klotho expression and tubulointerstitial fibrosis ($r=-0.69$, $p<0.01$), tissue angiotensinogen expression ($r=-0.77$, $p<0.01$), and urinary 8-OHdG excretion ($r=-0.64$, $p<0.01$).

Conclusion : Klotho gene is regulated by the RAS in chronic CsA nephropathy, and the regulation is mediated by resistance to oxidative stress.

Key Words : 사이클로스포린 , Klotho, 레닌-안지오텐신 시스템
Cyclosporine, Klotho, Renin-angiotensin system