P190

hypoxia inducible factor-1a의 활성화가 renal tubule cell에서 NFkB dependent inflammation을 호전시키는가

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Hypoxia Inducible Factor-1α Attenuates NFκB-dependent Inflammation in Renal Tubule Cells

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Purpose: Renal inflammation is an invariable pathologic finding in almost all forms of chronic kidney disease irrespective of its cause. Hypoxia-inducible factor (HIF) is a transcription factor that regulates cellular hypoxic responses. The activation of HIF has been proved to be effective in various kidney disease models. The aim of this study is to investigate the anti-inflammatory mechanism of HIF in renal tubular epithelial cells.

Methods: Renal tubular epithelial cells (HK-2 cells) were exposed to tumor necrosis factor-α (TNF-α) at 5 ng/mL and interferon-γ (INF-γ) at 50 ng/mL for 24 hours, and cobalt chloride (CoCl2) 150 μM was added. The RANTES (Regulated upon Activation, Normal T cell expressed and Secreted), MCP-1 (monocyte chemoattractant protein-1) levels were investigated by enzyme-linked immunosorbent assay. Nuclear factor kappa B (NFκB) p65, phosphorylated NF-κB p65, inhibitor of NF-κB (IκB)α, phosphorylated IκBα were determined by western blotting. NF-κB p50 DNA binding was detected by ELISA using Transfactor p50 kit. NF-κB transcription activity was evaluated by luciferase reporter gene assay.

Results: Stimulation of HK-2 cells by combination of TNF-α and INF-γ for 24hrs results in strong production of RANTES (813.0±21.7 pg/mL) and MCP-1 (305.9±91.4 pg/mL), these levels were decreased by pre-treatment of pyrrolidine dithiocarbamate 10 mM (190.1, 131.2 pg/mL, respectively), and also attenuated by CoCl2 treatment (RANTES, 242.9±187.2 pg/mL, $p<0.001$; MCP-1, 65.5±21.6 pg/mL, $p=0.001$).

Combination of TNF-α and INF-γ induced NFκB p65 phosphorylation, it was attenuated by CoCl2 treatment in nuclear fraction ($p=0.023$). Combination of TNF-α and INF-γ caused decreased expression of IκBα and it was recovered in cells with CoCl2 treatment ($P<0.001$). NF-κB p50 DNA binding activity in HK-2 cell treated for TNF-α and INF-γ was 1.8-fold, in the presence of CoCl2 was 1.4-fold, compared with control ($p=0.039$). Luciferase reporter gene assay showed that TNF-α and INF-γ increased NF-κB transcription activity by 8.1 fold, and the increased transcription activity decreased to 4.5-fold by addition of CoCl2, compared with the control ($p<0.001$).

Conclusion: Treatment of CoCl2 attenuates cytokine production of RANTES and MCP-1, phosphorylation of NFκB p65 and degradation of IκBα. These data suggest that HIF-1α attenuate TNF-α and INF-γ induced inflammation, by preventing degradation of IκBα in renal tubular cells.

Key Words: 저산소증, 염증, NF-kappa B
Hypoxia-inducible factor 1, NF-kappa B, Inflammation