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STAT3/CCR5 면역신호 조절을 통한 신장 허혈-재관류 손상 억제 효과

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STAT3/CCR5 Signal Regulation Mitigates Renal Ischemia-Reperfusion Injury

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Signal transducer and activator of transcription3 (STAT3) is unique transcription factor and known for a key member of the JAK-STAT signaling pathway. STAT3 was recently revealed to play roles in chemokine receptor 5 (CCR5) expression in human monocytes. CCR5 promoter regions contain STAT3 binding sites. In kidney disease, its role is unclarified. Therefore, we studied the interaction of STAT3 and CCR5 signals on renal ischemia-reperfusion injury (IRI). B6 wild type and CCR5 KO mice were performed in bilateral renal artery pedicles clamping for 30 min followed by reperfusion. After then, we quantified intrarenal cytokine expression using real-time PCR. Moreover, we cultured human tubular epithelial cells (TEC) in hypoxic condition and evaluated the effect of caffeic acid 3,4-dihydroxyphenethyl ester (CADPE, JAK2/STAT3 inhibitor) treatment. IRI produced more severe tubular damage in B6 wild type mice than in CCR5 KO mice (BUN, 191.0±2.7 vs. 176.3±2.3 mg/dL; creatinine, 2.37±0.04 vs. 1.75±1.16 mg/dL, $p<0.05$). Although inflammatory cytokines/chemokines, such as monocyte chemotactic protein-1, IL-1β, CCR5, CCL4, and CCL5 were increased by IRI in wild type mice compared to sham mice, they were significantly attenuated in CCR5 KO mice. The expression of STAT3α as well as total STAT3 was more reduced in CCR5 KO mice than in wild type mice, whereas STAT3β level was not different between the two groups. These findings were supported by in vitro study with human TEC. The level of CCR5 and pSTAT3 were elevated in the hypoxia-conditioned TECs, however, decreased in CADPE treated cells. We demonstrated that the activation of CCR5 via STAT3 (dominantly STAT3α) may be associated with progression of ischemia-reperfusion injury. These mechanisms of STAT3/CCR5 signaling suggest a novel strategy for management of acute kidney injury with STAT3 inhibitor.

Key Words: 허혈재관류 손상, STAT3, CCR5
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