

급성신부전 모델에서 IL-2/항IL-2 항체 복합체의 조절T세포를 통한 신보호효과

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IL-2/anti-IL-2 Antibody Complexes Attenuate Renal Ischemia-reperfusion Injury Through Expansion of Regulatory T Cells

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Background: Regulatory T cells (Tregs) can contribute to suppression of immunologic damage or facilitation of the recovery process following renal ischemia-reperfusion injury (IRI). However, isolation and expansion of rare Tregs are practically hard for clinical application. Recently, complexes (IL-2C) of interleukin-2 (IL-2) and anti-IL-2 antibodies have been shown to control various inflammatory diseases by inducing expansion of Tregs. Therefore, we investigated whether IL-2C can control renal IRI.

Methods: C57BL6/J mice underwent bilateral renal ischemia. IL-2C were administered for 3 consecutive days from 5 days before or 1 day after renal IRI. Induction of Tregs was analyzed in kidney and spleen. Renal function (BUN, creatinine), histological renal damage (PAS, TUNNEL staining), inflammatory cell infiltration (immunohistochemistry), tissue cytokine expression (multiplex bead array) and tissue recovery (PCNA staining) were assessed. Next, anti-CD25 antibodies (PC61) were administered together with IL-2C, in order to investigate whether Treg depletion can abrogate impacts of IL-2C.

Results: IL-2C induced a 5-10 fold increase of Tregs in both spleen and kidney. IL-2C treatment before renal IRI improved renal function (Cr, 2.2 ± 0.7 vs 1.2 ± 0.7 mg/dL, $p=0.0086$), attenuated histological renal injury (tubular injury score, 2.2 ± 0.3 vs 1.5 ± 0.1 , $p=0.036$) and apoptosis (TUNEL positive cells, 18.5 ± 3.5 vs 9.8 ± 2.2 /HPF, $p=0.029$). Tubular cell proliferation also increased (PCNA positive cells, 8.4 ± 0.1 vs $10.0 \pm 0.7\%$, $p=0.021$). MCP-1 and IL-6 was suppressed by IL-2C. Analysis of innate and adaptive immune cell infiltration is ongoing. Depletion of Tregs using PC61 abrogated the beneficial effects of IL-2C on renal IRI (Cr, 1.1 ± 0.2 vs 1.7 ± 0.2 , $p=0.035$). Although IL-2C treatment after renal IRI did not improve renal apoptosis or damage, tubular cell proliferation significantly increased (PCNA positive cells, 14.0 ± 1.8 vs $21.6 \pm 3.8\%$, $p=0.041$).

Conclusion: IL-2 complexes attenuated acute renal damage in injury phase and facilitated renal recovery in recovery phase of renal IRI, by inducing Tregs. IL-2C is promising for clinical application to renal IRI.

Key Words: 조절T세포, IL-2복합체, 급성신부전

Regulatory T cells, IL-2 complex, Acute kidney injury