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Protective Effect of Macrophage Depletion by Liposome Clodronate on Long Term Change Induced by Acute Renal Ischemic/reperfusion Injury

고려대학교 의과대학 내과학교실, 신장병연구소

고강지 · 장경현* · 이재원 · 현영율 · 최혜민 · 부창수 · 조상경 · 조원용 · 김형규

Background : Renal ischemic/reperfusion (I/R) injury is a major cause of acute intrinsic renal failure. Recently, more attention has been focused on long term effects of I/R injury, especially in the transplanted kidney. Persistent inflammatory response is considered importantly in the long term change by acute I/R injury, but its exact mechanism and the role of macrophage are still unknown. So we aimed to investigate the role of macrophage on the long term renal function change after acute I/R injury by depletion of macrophage with liposome clodronate (LC).

Methods : Male Sprague-Dawley rats were underwent right nephrectomy or sham ischemia on 1st day and occlusion on left renal vascular pedicle for 50 mins on 5th day. LC or liposomal vehicle were injected for 4-8 wks every 5 days from 8th day. Biochemical and histological renal damage were assessed and gene expression kinetics such as tumor necrosis factor-alpha (TNF-α), monocyte chemoattractant protein-1 (MCP-1) using quantitative real time reverse transcription-polymerase chain reaction were conducted at 4 and 8weeks.

Results : The percentage of ED-1 positive cells in liver decreased significantly in LC-treated group at 4,8weeks. Systemic monocyte-macrophage depletion resulted in reduced tubulointerstitial fibrosis, collagen deposit and loss of tubular architecture. Decreased creatinine clearance and increased urinary protein clearance compared to sham control were shown in vehicle group at 8 weeks (1,561.8 vs 2,656.4 mL/d, p=0.016, 225% vs 100%, p=0.016), and this change were diminished by LC treatment (2,096 mL/d, p=0.05, 108%, p=0.026). This beneficial effect was accompanied by a significant decrease of IL-1β, MCP-1 and TNF-α gene expression.

Conclusion : Persistent change in tubular structure and collagen deposit occur after single episode of severe I/R injury. These progressive structural change and renal function decrease were reduced by systemic macrophage depletion. It suggests that macrophage contribute to tubulointerstitial fibrosis in the maintenance period after acute I/R injury.