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Macrophage Depletion by Liposomal Clodronate Reduces Ischemia/reperfusion Injury in Rats

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Background : Although neutrophils and T cells play an important role in renal injury following ischemia/reperfusion, the role of macrophages is still unknown. Using Liposomal clodronate (LC) that can deplete macrophages from liver, spleen and peripheral blood (PB), we examined the role of macrophages in ischemic acute renal failure (ARF) in rats.

Methods : 1 mL of LC or liposomal vehicle (LV) were iv injected 24 hrs before ischemia in male Sprague-Dawley rats and underwent bilateral renal pedicle clamping (40 min) or sham ischemia. Biochemical and histological studies were done and the kinetics of TNF-α, IL-1β, IL-6 gene expression levels using quantitative real time RT-PCR was done at 4, 24, 72 hrs.

Results : Percentage of peripheral blood monocytes decreased significantly in LC treated group (6.4 ± 0.1 vs $0.98\pm0.2\%$, $p<0.01$) at 24 hrs. ED-1 positive mononuclear cell infiltration increased markedly at 24 hrs after ischemia/reperfusion and LC treatment significantly reduced interstitial mononuclear cell infiltration with functional and histological protection. Apoptosis, mostly occurred in distal tubules also decreased significantly in LC treated animals. Gene expression kinetics showed that IL-6 gene expression peaked early at 4hrs after reperfusion, followed by TNF-α, IL-1β expression, peaking at 24 hrs. LC treatment significantly reduced these cytokine gene expression levels at each time point, indicating that infiltrating macrophages are responsible for the production of proinflammatory cytokines and subsequent renal injury in ischemia/reperfusion induced ARF.

Conclusion : ED-1 positive mononuclear cells play a pivotal role in tubular cell injury by producing various proinflammatory cytokines in ischemia/reperfusion injury.