

## 중성구의 세포사멸이 허혈/재관류에 의한 급성 신손상의 회복기에 미치는 영향

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### Inhibition of Neutrophil Apoptosis Delay Recovery Process in Ischemia/reperfusion Induced Acute Kidney Injury

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Ischemia/reperfusion (I/R) induced acute kidney injury (AKI) is characterized by intense neutrophilic inflammation and it substantially contributes to pathogenesis of AKI. Although it is assumed that resolution of inflammation is a prerequisite for complete restoration of normal tissue function or for preventing transition to chronic kidney disease, precise mechanisms underlying the resolution of inflammation in I/R induced AKI remain elusive. The purposes of this study were to examine 1) whether apoptosis is primary way of eliminating neutrophils in resolution phase of AKI and 2) the effect of neutrophil apoptosis in kidney regeneration and recovery.

We generated Bax KO bone marrow chimera (Bax KO BM→WT) by transplanting bone marrows from Bax KO mice to sublethally irradiated WT mice in whom only bone marrow derived cells have resistance to apoptosis. Thirty minutes bilateral I/R was done and mice were sacrificed at day 1, 2, and 5 days and various biochemical, histologic analyses were done.

Generation of Bax KO BM chimera was confirmed by genomic DNA analysis from peripheral blood. In experiments for characterization of immune cells, splenocytes from Bax KO mice showed diminished apoptosis against H2O2 stimuli, while their innate immune activation or migratory capacity toward monocyte chemoattractant peptide-1 (MCP-1) were comparable with those from WT mice. On day 2 after I/R in WT mice, annexin V positive apoptotic neutrophils were observed. Despite similar degree of initial neutrophil influx or functional, histologic kidney injury, Bax KO BM chimeric mice showed persistent neutrophilic inflammation and significantly delayed functional, histologic kidney recovery compared to WT BM→WT control mice. In addition, kidneys from Bax KO BM chimeric mice showed persistently increased level of proinflammatory cytokines and also significantly decreased number of proliferating cell nuclear antigen (PCNA) positive cells.

Our results present first evidence that neutrophil apoptosis is critical step in resolution of inflammation in I/R induced AKI and also might serve as a prerequisite for kidney regeneration or restoration of normal tissue function.

**Key Words:** 급성신부전, 세포사멸사, 중성구

Acute kidney injury, Apoptosis, Neutrophil