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oxidized adenosine triphosphate의 purinergic system을 통한 허혈-재관류 신손상 조절

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Control of Puringergic System by Oxidized Adenosine Triphosphate Protects the Kidneys Against Ischemia-reperfusion Injury

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Background: Extracellular adenosine triphosphate (ATP) plays a crucial in promoting inflammatory immune responses. The extracellular ATP can stimulate both innate immune cells such as dendritic cells (DCs), macrophages, and adoptive immune cells such as effector T cells through P2X receptor, and can also suppress regulatory T cells (Tregs). Oxidized ATP (oATP) is a P2X receptor antagonist. Here, we investigated whether oATP can attenuate renal ischemia-reperfusion injury (IRI), an acute inflammatory condition.

Methods: Bilateral renal IRI was induced in wild type and RAG-1 knockout (KO) C57BL/6 mice. oATP or PBS was administered to the mice for 7 consecutive days beginning 6 days before IRI in a prevention model, or 4 consecutive days beginning 1 day after IRI in a treatment model.

Results: In the prevention model, both serum BUN and creatinine on day 1 were significantly lower in the oATP group than in the PBS group (P=0.001, $p<0.001$). Both tubular injury score and tubular epithelial cell apoptosis were also significantly lower in the oATP group ($p<0.001$, p=0.001). oATP significantly attenuated the infiltration of MHC II+, CD40+, or CD86+ DCs, neutrophils and macrophages into the renal tissue after IRI. It decreased infiltration of CD69+CD4+ and CD44+CD4+ T cells, while increased infiltration of Foxp3+CD4+ Tregs in renal tissue. Expression of IL-6 and CCL2 was reduced in the oATP group. Treg depletion using PC61 abrogated the beneficial effects of oATP. These data suggested that Treg induction is an important mechanism of oATP's beneficial effects. oATP also decreased infiltration of innate immune cells, and attenuated renal functional deterioration (p=0.003 for BUN, p=0.001 for creatinine) after IRI in RAG-1 KO mice as well as wild type mice. These data suggested that oATP can partially attenuate renal IRI by suppressing innate immunity independently of effector T cells or Tregs. In the treatment model, renal function on day 5 was significantly better in the oATP group than the PBS group (p=0.005 for BUN, p=0.007 for creatinine). oATP decreased infiltration of innate and adaptive effector cells, and increased infiltration of Foxp3+ CD4+ Tregs in renal tissue. In addition, oATP increased renal tubular cell proliferation on day 5 (p=0.013) and reduced renal fibrosis on day 28 (p=0.001).

Conclusion: oATP can attenuate acute renal damage, and improve renal recovery in IRI by suppressing both innate and adaptive immune cells, and inducing Tregs.

Key Words: Oxidized ATP, 허혈-재관류 신손상, 조절 T세포
Oxidized ATP, Ischemia-reperfusion injury, Regulatory T cells