

## 허혈-재관류 손상에 대한 oxidized adenosine triphosphate의 신장 보호 효과

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### Oxidized Adenosine Triphosphate Protects the Kidneys Against Ischemia-reperfusion Injury

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**Background:** Extracellular adenosine triphosphate (ATP) plays a crucial role in promoting inflammatory immune responses. The extracellular ATP can stimulate effector T cells as a costimulatory signal through P2X receptor, and oxidized ATP (oATP), a P2X receptor antagonist, can induce regulatory T cells (Tregs). Tregs can suppress inflammatory processes and thereby renal injury in ischemia-perfusion injury (IRI). Here, we investigated whether oATP can attenuate renal IRI by inducing Tregs in murine models.

**Methods:** Male C57BL/6 mice, 6-8 weeks old, were used in both prevention and treatment models. The core temperature was maintained at 37°C with heating pad, and both renal pedicles were clamped for 28 minutes. oATP or PBS was administered intraperitoneally to the mice for 7 consecutive days beginning 6 days before IRI, or 4 consecutive days beginning 1 day after IRI. Serum blood urea nitrogen (BUN) and creatinine (Cr) were measured to assess kidney function. Flow cytometric analysis of spleen and kidney cells was conducted. Renal inflammation was assessed using immunohistochemical staining and tissue cytokine quantification.

**Results:** Low-dose multiple injection of oATP induced more CD4+CD25+ Tregs than high-dose once injection of oATP ( $p=0.001$ ), and therefore we chose low-dose multiple injection of oATP in order to induce Tregs. In the prevention model, oATP induced significant expansion of CD4+CD25+ Tregs in the spleen ( $p=0.009$ ). Both serum BUN and Cr were significantly lower in the oATP group than in the PBS group ( $p=0.001$  and  $p<0.001$ , respectively). Both tubular injury score and tubular epithelial cell apoptosis after IRI were significantly lower in the oATP group than in the PBS group ( $p<0.001$  and  $p=0.001$ , respectively). oATP also significantly attenuated the infiltration of both neutrophil and macrophage into the renal tissue after IRI ( $p<0.001$  for both), and decreased the expression of both IL-6 and CCL2 ( $p=0.021$  for both). In the treatment model, oATP induced significantly expansion of CD4+CD25+ Tregs in the spleen and kidney ( $p<0.001$  and  $p=0.016$ , respectively). Renal function on day 5 was significantly better in the oATP group than the PBS group ( $p=0.005$  and  $p=0.007$ , respectively). In addition, renal tubular cell proliferation on day 5 was significantly increased by oATP ( $p=0.013$ ).

**Conclusion:** oATP can attenuate acute renal damage, and improve renal recovery in IRI by inducing Tregs.

**Key Words:** Oxidized ATP, 허혈-재관류 신손상, 조절 T 세포  
Oxidized ATP, Ischemia-reperfusion injury, Eglulatory T cells