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Oxidized adenosine triphosphate, a P2X7 receptor antagonist, ameliorates renal ischemia-reperfusion injury through expansion of regulatory T cells

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Objectives : Extracellular adenosine triphosphate (ATP) binds to purinergic receptors and, as a danger molecule, promotes inflammatory responses. We investigated whether periodate-oxidized ATP (oATP), a P2X7 receptor (P2X7R) antagonist can attenuate renal ischemia-reperfusion injury (IRI) and attempted to elucidate related cellular mechanisms.

Methods : Bilateral renal IRI was induced in wild-type, RAG-1 KO and P2X7R knockout mice. oATP or PBS was intraperitoneally injected for 7 consecutive days staring 6 days prior to IRI in the prevention model, and for 4 consecutive days starting 1 day after IRI in the treatment model. Blood, kidney, and spleen were harvested 1 day after IRI in the prevention model, and 5 and 28 days after IRI in the treatment model.

Results : oATP treatment prior to IRI decreased blood urea nitrogen and serum creatinine after IRI. The renal tubular injury and apoptosis was also decreased by oATP. oATP attenuated the infiltration of dendritic cells, neutrophils, macrophages, and CD69+CD4+ and CD44+CD4+ T cells while increasing renal infiltration of Foxp3+CD4+ regulatory T cells (Tregs). The expression levels of IL-6 and CCL2 were reduced in the oATP group. Next, oATP treatment after IRI improved renal function, decreased the infiltration of innate and adaptive effector cells, and increased the renal infiltration of Foxp3+CD4+ Tregs. Post-IRI oATP treatment increased tubular cell proliferation and reduced renal fibrosis. oATP attenuated renal functional deterioration after IRI in RAG-1 knockout mice; however Treg depletion using PC61 abrogated the beneficial effects of oATP in wild-type mice. Renal IRI was also attenuated in P2X7R knockout mice as well as the treatment of the antagonist, oATP. P2X7R expression was induced in both immune cells including macrophages, dendritic cells and T cells, and non-hematopoietic cells in the kidney after IRI. Bone marrow chimera experiments demonstrated that P2X7R expression on hematopoietic cells rather

than on non-hematopoietic cells (such as tubular epithelial cells) plays a major role in IRI. Furthermore, oATP treatment after transfer of wild-type Tregs improved beneficial effects of Tregs on IRI, whereas oATP treatment after transfer of P2X7R knockout Tregs did not. In addition, Tregs of P2X7R knockout mice showed more beneficial effects on renal IRI than Tregs of wild-type mice.

Conclusions : oATP attenuated acute renal damage and facilitated renal recovery in IRI through expansion of Tregs and suppressing both innate and adoptive effector cells. Clinical application of purinergic inhibitors is promising for prevention and treatment of renal IRI.

Keywords : innate immunity, ischemia-reperfusion injury, periodate-oxidized adenosine triphosphate, purinergic receptor, regulatory T cells