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Role of purinergic system in renal ischemia-reperfusion injury

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Extracellular adenosine triphosphate (ATP) binds to purinergic receptors and, as a danger molecule, promotes inflammatory responses. As time goes on, ectonucleases such as CD73 and CD39 convert ATP to adenosine, which binds to adenosine receptor and regulates inflammatory responses. Adenosine agonist abrogated renal ischemia-reperfusion injury (IRI) through regulatory T cells. Next, we investigated whether periodate-oxidized ATP (oATP), a P2X7 receptor (P2X7R) antagonist can attenuate renal IRI and elucidated the related cellular mechanisms. oATP treatment prior to IRI decreased BUN and serum creatinine after IRI. The tubular injury score and tubular epithelial cell apoptosis were 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+ Tregs. The expression levels of IL-6 and CCL2 were reduced in the oATP group. oATP treatment after IRI also 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. 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. Renal IRI was attenuated in P2X7R knockout mice. Bone marrow chimera experiments demonstrated that P2X7R expression on hematopoietic cells rather than non-hematopoietic cells, such as tubular epithelial cells, plays a major role in IRI. In conclusion, oATP attenuated acute renal damage and facilitated renal recovery in IRI through expansion of Tregs.