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IL-2/Anti-IL-2 complex attenuates renal cold ischemia reperfusion injury after kidney transplantation through expansion of regulatory T cells.

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Objectives: Cold ischemic reperfusion injury (IRI) is an inevitable complication that affects graft outcomes after kidney transplantation. IL-2/Anti-IL-2 complex (IL-2C), *in vivo* Treg inducer, was reported to attenuate renal warm IRI. However, its protective effects on cold IRI, stronger renal injury than warm IRI, remain unknown.

Methods: Donor C57BL6/J mouse kidneys were preserved in cold HTK solution and then transplanted to syngeneic recipients along with bilateral nephrectomy. Recipients received IL-2C before or after kidney transplantation. Renal functions were measured by plasma creatinine, BUN, and Kim-1. Renal fibrosis was measured by MT staining and expression of type IV collagen, fibronectin, and α-SMA.

Results: Cold ischemic time (CIT) > 7h induced high mortality, whereas CIT < 5h did not induce significant renal injury. Plasma creatinine levels after CIT of 5h and 6h were 1.313±0.668 and 2.153±0.830, respectively. Warm ischemic time (WIT) ≤ 22min induced weak renal injury, whereas WIT ≥ 26min induced high mortality. Our final cold IRI model consisted of 5h CIT and 24min WIT. Cold IRI aggravated renal functions and induced renal fibrosis to greater extent than warm IRI with 0h CIT. Adoptive transfer of regulatory T cells (Tregs) attenuated renal injury by cold IRI. Administration of IL-2C prior to cold IRI increased renal Tregs and attenuated renal functional deterioration as well as histologic tubular injury score on day 1 and 7. IL-2C also suppressed renal infiltration of macrophages and neutrophils, and expression of IL-1β, MCP-1, and TNF-α. Renal fibrosis was attenuated by IL-2C on day 28. Next, IL-2C administration following cold IRI also improved renal functions on day 7. Furthermore, depletion of Tregs with anti-CD25 antibodies, abrogated the beneficial effects of IL-2C on cold IRI.

Conclusions: IL-2C attenuates acute renal injury and chronic renal fibrosis in cold IRI after kidney transplantation through induction of Tregs. IL-2C has a therapeutic potential for cold IRI.