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# Substance P Improves Renal Ischemia Reperfusion Injury through Modulating Immune Response

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**Objectives:** Substance P (SP), an injury-inducible messenger that mobilizes bone marrow stem cells and modulates the immune response, has been suggested as a novel target for therapeutic agents. We evaluated the role of SP as an immune cell modulator during the progression of renal ischemic/reperfusion injury (IRI).

**Methods:** A unilateral renal IRI model was established using 8-week-old male C57BL/6 mice. We induced ischemia in the left kidneys of the mice using a microclamp to obstruct blood circulation for 45 minutes. To evaluate the effects of IRI on mobilization and homing of bone marrow-derived cells to injured kidneys, we performed FACS analysis at 1 and 3 days after IRI. To demonstrate the effect of SP on AKI to CKD progression, SP was administered via the tail vein twice per week for 4 weeks at 1 week after IRI. We perfermed histological analysis at 5 weeks after IRI

**Results:** Unilateral IRI induced the transient expression of endogenous SP and the infiltration of CCR7+ M1 macrophages in injured kidneys. However, SP altered the intrarenal macrophage polarization from CCR7+ M1 macrophages to CD206+ M2 macrophages in injured kidneys. SP also modulated bone marrow-derived neutrophils and mesenchymal stromal cells after IRI. SP treatment for 4 weeks starting one week after unilateral IRI significantly preserved kidney size and length and normal tubular structures and alleviated necrotic tubules, inflammation, apoptosis and tubulointerstitial fibrosis. The beneficial effects of SP were accompanied by attenuation of intrarenal recruitment of CD4, CD8 and CD20 cells and abnormal angiogenesis.

**Conclusions:** The immunomodulatory effect of SP suggested that SP could be a promising therapeutic target for preventing the progression of acute kidney injury to chronic kidney disease.