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Temporal changes of cellular senescence in post-acute kidney following ischemia-reperfusion

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Objectives: Renal ischemia-reperfusion (IR) injury is linked to progression of chronic kidney disease, and can be related to cellular senescence. However, the impact of senescence at each time point after IR remains unclear. We sequentially studied cellular senescence of murine kidneys after IR.

Methods: Renal IR injury was induced by unilateral clamping of the right renal pedicle for 30 minutes in C57BL/6 mice. At the different time points after surgery (2, 4, 6, and 8 weeks, n=8-10 each), renal function, senescence, inflammation, and histology were evaluated ex vivo.

Results: The ratio of right to left kidney was gradually decreased from 4 weeks onwards after IR injury compared to sham and 2 weeks. Plasma creatinine and cystatin C levels were elevated at 8 weeks after IR. Renal gene expression of senescence (*Cdkn2a* and *Cdkn1a*) and its secretory phenotype (*Mmp3, Tnfa, Tgfβ, Il6, Il1a, Serpine1,* and *Ccl2*) were upregulated at 2 weeks after IR compared to sham and persisted up to 8 weeks. Tubular injury and tubular epithelial senescence increased after 2 and 4 weeks of IR, whereas kidneys at 6 and 8 weeks after IR showed elevated fibrosis and inflammation as well as senescence of interstitial cells.

Conclusions: Post-acute kidney following ischemia-reperfusion increased tubular epithelial senescence in the early phase and senescence of interstitial cells thereafter. These observations support development of senotherapy in preventing the transition to chronic kidney disease after ischemic acute kidney injury.