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CD137L signaling is a checkpoint in renal inflammation.

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Objectives: Inflammation and repair are closely linked. We have previously shown that signaling via CD137 ligand (CD137L) promotes renal inflammation occurring after ischemia-reperfusion injury by inducing production of neutrophil-recruiting chemokines from tubular epithelial cells. In this study, we provide evidence showing that CD137L signaling enhances resolution of renal inflammation and renal tissue repair.

Methods: We used mouse ischemia-reperfusion injury model and unilateral ureteral obstruction model.

Results: Administration of CD137-Fc fusion protein 24 hours after renal ischemia-reperfusion injury increased Arginase-expressing macrophages and proliferation of tubular epithelial cells. RNA seq analysis of bone marrow-derived macrophages (BMDMs) showed decreased expression of inflammatory genes and increased expression of anti-inflammatory genes. Interestingly, GM-CSF and CD137-Fc synergistically suppressed transcription-controlling genes and promoted transcription of genes involved in negative regulation of cell proliferation. RNA seq analysis also demonstrated the rewiring of glycolysis and TCA cycle by GM-CSF and CD137L co-signaling in BMDMs. Finally, we showed that absence of CD137L signaling had uncontrollable chronic renal inflammation in the unilateral ureteral obstruction model.

Conclusions: Taken together, our results suggest that CD137L signaling is critical in resolution of tissue inflammation.