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ACUTE KIDNEY INJURY

SOCS-3 EXPRESSION DETRIMENTAL IN AKI

Transgenic mice with targeted deletion of suppressor of cytokine signalling 3 (SOCS-3) in renal proximal tubules have better kidney function following acute kidney injury (AKI) than their wild-type littermates, according to a new study by Roland Schmitt and colleagues from Hannover Medical School, Germany.

AKI is characterized by tubular cell damage and the subsequent infiltration of mononuclear cells that include macrophages—processes controlled by the action of growth factors and cytokines, of which SOCS-3 is a key regulator. In two models of AKI—aristolochic acid nephropathy and ischaemia–reperfusion injury—the researchers observed markedly increased proximal tubular expression of SOCS-3 mRNA. The functional significance of this upregulation in AKI was tested by generating mice with conditional deletion of SOCS-3 in renal proximal tubules, the kidney region most prone to damage during injury. In both AKI models, *Socs3*$^{PT-/-}$ mice had better renal function than wild-type mice, as shown by lower serum creatinine and urea levels. Improved renal function in the *Socs3*$^{PT-/-}$ mice was associated with increased reparative tubular cell proliferation, mediated by enhanced Stat3 signalling.

Surprisingly, kidneys from *Socs3*$^{PT-/-}$ mice with AKI had significantly higher numbers of macrophages than did those from wild-type mice with AKI. Macrophage population analysis revealed altered polarization, from a classically activated (proinflammatory) to an alternatively activated (reparative) phenotype. Thus, modulation of macrophage phenotype, coupled with increased mitogenic Stat3 signalling and tubular proliferation, might account for the improved reparative response observed in kidneys from *Socs3*$^{PT-/-}$ mice.

As Schmitt speculates, "SOCS-3 and/or other candidate factors that are involved in the crosstalk between injured parenchymal cells and cells of the immune system might become important new targets for novel therapeutic strategies in AKI." However, evidence that knockout of *Socs3* in macrophages actually promotes proinflammatory polarization highlights the need for strategies targeting SOCS-3 to be cell-type-specific.

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Original article Susnik, N. *et al*. Ablation of proximal tubular suppressor of cytokine signaling 3 enhances tubular cell cycling and modifies macrophage phenotype during acute kidney injury. *Kidney Int*. doi:10.1038/ki.2013.525