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Inhibition of STAT3 mitigates inflammation of renal ischemia-reperfusion injury through downregulating apoptosis

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Objectives: Signal transducer and activator of transcription 3(STAT3) is a latent cytoplasmic transcription factor that plays critical roles in inflammatory environment. The role of STAT3 is not well established in AKI and the mechanism by which it contributes to CKD.

Methods: Renal IR(ischemia-reperfusion) injury was induced in B6 wild type mice. Stattic(a nonpeptide inhibitor of STAT3 activation) was treated 3 hours prior to IR injury. We quantified intrarenal cytokine expression using qPCR and Western blot, and performed FACS analysis. We cultured human tubular epithelial cells(TECs) in hypoxic condition and evaluated the effect of Stattic treatment. Apoptosis was quantified using Tunel assay and Annexin V/propidium iodide(PI) staining assay.

Results: IR injury produced more severe tubular damage and higher mortality in control group than in Stattic-treated mice. Although inflammatory cytokines and pSTAT3 were increased by IR injury, they were attenuated with Stattic-treatment. Tunel assay revealed that STAT3 inhibition decreased apoptosis. These findings were supported by in-vitro study with human TECs and immunohistochemistry of human ATN and CKD tissues. The cellular expression of pSTAT3,IL-6 and 8 were decreased in dose-dependent manner with Stattic-treatment. STAT3 inhibition also decreased the expression of apoptosis marker in dose-dependent manner. Annexin V/PI staining assay showed that STAT3 inhibition also decreased the apoptotic cells which were increased under the hypoxic condition. Expression of pSTAT3 was increased in human ATN tissue and it was positively correlated with serum creatinine. Also,increased expression of pSTAT3 in human CKD tissue was positively correlated with serum creatinine and urinary protein/creatinine ratio and CKD stages. These data were supported by rat 5/6 nephrectomy model. As fibrosis progressed, pSTAT3 expression was increased.

Conclusions: We demonstrated that the activation of STAT3 is associated with progression of IR injury through apoptosis and also contributes to chronic change from AKI. These mechanisms suggest a novel strategy for management of AKI with STAT3 inhibitor.