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Inhibition of CXCR3 expression through blockade of STAT3 alpha signaling down-regulate inflammation of renal ischemia-reperfusion injury

Jae Yoon Park[1], Kyung Don Yoo[2], Jae Wook Lee[5], Sung Joon Shin[1], Kyung Soo Kim[1], Yon Su Kim[3], Seung Hee Yang[4]
[1]Department of Internal Medicine-Nephrology, Dongguk University Ilsan Hospital, Korea, Republic of
[2]Department of Internal Medicine-Nephrology, Dongguk University Gyeongju Hospital, Korea, Republic of
[3]Department of Internal Medicine, Seoul National University College of Medicine, Korea, Republic of
[4]Department of Kidney Research Institute, Seoul National University College of Medicine, Korea, Republic of
[5]Department of Internal Medicine-Nephrology, National Cancer Center, Korea, Republic of

Objectives: Signal transducer and activator of transcription 3 (STAT3) is the main mediator of interleukin 6 (IL-6)–type cytokine signaling. Although it exists in two isoforms: the full-length STAT3α and the truncated STAT3β, their role in acute kidney injury is not clarified. We investigated their relative function through inhibiting STAT3α in ischemia-reperfusion (IR)-induced renal inflammation.

Methods: IR injury was induced in B6 wild type mice. Stattic (nonpeptide small molecular inhibitor of STAT3 activation and dimerization) was treated 3 hours prior to IR injury. We quantified intrarenal cytokine expression using real-time PCR and performed FACS analysis. We cultured human tubular epithelial cells (TECs) in hypoxic condition and evaluated the effect of Stattic treatment. We detected the isoforms of phosphorylated STAT3 using western blot analaysis.

Results: IR injury produced more severe tubular damage in control group than in Stattic-treated mice (serum creatinine, 2.2±0.1 versus 1.6±0.1 mg/dL, $p<0.05$). Although inflammatory cytokines/chemokines, such as IL-6, total STAT3, STAT3α, CXCR3, IL-10 and TGF-β were increased by IR injury in control group, they were attenuated in Stattic-treated mice. Apoptosis of TECs and infiltration of mononuclear cells and macrophages were decreased and the expression of STAT3α as well as total STAT3 was reduced in Stattic-treated mice. These findings were supported by in-vitro study with human TECs. Whereas the level of pSTAT3α was elevated in hypoxia-conditioned TECs and it was decreased in Stattic-treated cells, the level of pSTAT3β was not changed in both cell groups. The expression of CXCR3 was decreased in accordance to the STAT3α decrease and the supernatant levels of IL-6 and IL-8 were decreased in Stattic-treated cells.

Conclusions: We demonstrated that activation of STAT3 is associated with progression of IR injury and the α-isoform may contribute as major player. These mechanisms of STAT3/CXCR3 signaling according to each isoforms suggest a novel strategy for management of AKI with STAT3 inhibitor.