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Inhibition of toll-like receptor 4 ameliorates kidney ischemia-reperfusion injury

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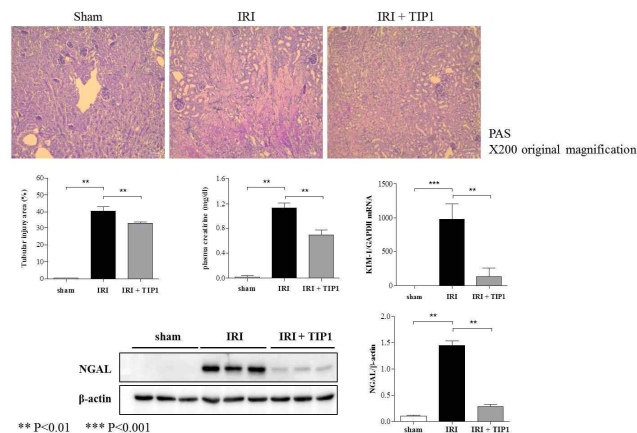
Objectives: Renal ischemia-reperfusion injury is a key mechanism in various clinical settings including sepsis and transplantation. While animal studies have demonstrated that toll-like receptor (TLR) 4 signaling is a major mediator induced by ischemia-reperfusion injury, the effect of pharmacologic inhibition of TLR4 on this injury has not been studied.

Methods: We investigated the effects of TLR4 blockade in mice whose both renal arteries were clamped for 23 minutes and released. TLR inhibitory peptide (TIP) was injected intraperitoneally 30 minutes before the surgical procedure. To assess the effects of TLR4 inhibition on renal tubular epithelial cells, primary mouse renal tubular cells were incubated under hypoxia and subsequent reoxygenation with or without TIP.

Results: In mice subjected to ischemia-reperfusion injury, TIP pretreatment lowered an increase of serum creatinine levels and attenuated tubular injury. The beneficial effects of TLR4 blockade were associated with reduced intrarenal mRNA expressions of inflammatory cytokines, less development of apoptosis, and lowered oxidative stress. The flow cytometry also revealed that TIP pretreatment caused less infiltration of T helper 17 cells (Th17) into the kidneys. In primary tubular cell culture, the addition of TIP into culture media led to decreased expressions of KIM1 and inflammatory cytokines.

Conclusions: Our results indicate that inhibiting toll-like receptor 4 signaling pathway has a protective effect against ischemia-reperfusion injury by reducing tubular cell damage and Th17 infiltration.

TLR4 inhibition attenuates kidney ischemia-reperfusion injury



The effects of TLR4 blockade on inflammatory mediators and immune cells following kidney ischemia-reperfusion injury

