Role of the transcription factor STAT3 in the development of multiple organ injury in mice with cecal ligation and puncture-induced sepsis

Kengo Tomita, Samar Imbaby, Takuya Sakamoto, Yuichi Hattori

Department of Molecular and Medical Pharmacology, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Japan

Despite considerable progress in various antibiotic therapies, sepsis still has a high mortality rate. Sepsis has been now redefined as a life-threatening organ dysfunction due to a dysregulated response of the host to infection. Any definitive treatment for sepsis has not yet been established, and elucidation of the molecular mechanism of the sepsis pathology is an urgent issue. STAT3 (signal transducers and activator of transcription 3) is an inducible transcription factor activated by cytokines such as IL-6 and regulates the expression of many inducible genes involved in immune and inflammatory responses. Activation and expression of STAT3 are associated with various pathophysiological changes in each organ. However, the relationship between STAT3 signal and septic multiorgan injury is not known well. In this study, we investigated the role of STAT3 on the development of multiple organ injury in sepsis by testing the effect of the STAT3 inhibitor Stattic on dysfunction of key organs in mice with cecal ligation and puncture (CLP)-induced polymicrobial sepsis. Initially, we examined changes in mRNA levels of TNF-α, IL-1β, MCP-1, IL-6, and gp130 in lung, liver, kidney and heart. After induction of sepsis, mRNA expression levels of those inflammation-related genes greatly elevated in all tissues. Treatment with Stattic significantly inhibited of TNF-α, IL-1β, MCP-1, but not IL-6 and gp130, at 18 h after CLP. Next, we examined phosphorylation of STAT3 by using western blotting analysis. CLP-induced sepsis had a marked increase in its phosphorylation levels in different tissues. Although Stattic did not suppressed STAT3 phosphorylation, gel shift assay showed that Stattic eliminated an increase in STAT3 DNA binding activity in lung tissues following CLP-induced sepsis. Histopathological changes, which were assessed by H&E and myeloperoxidase staining, showed that CLP-induced sepsis resulted in each organ damage with marked influx of inflammatory cells. Treatment with Stattic prevented such histological damages in CLP-induced sepsis. These results indicate that STAT3 is involved in the development of major end-organ (that is, lung, kidney, and liver) injury in sepsis. We thus suggest the potential usefulness of STAT3 inhibition for septic multiple organ dysfunction.