〔目的〕

Sepsis is a major clinical challenge with unacceptably high mortality. In recent years, sepsis is regarded as a gene-related and gene therapy may be considered a promising novel therapeutic approach for treatment of sepsis. The signal transducers and activators of transcription (STAT) family of transcription factors is known to activate critical mediators of cytokine responses, and, among this family, STAT3 is implicated to be a key transcription factor in both immunity and inflammatory pathways. Growing evidences suggest that STAT3 is a major mediator of inflammation. However, little is known about the potential usefulness of STAT3 inhibition in sepsis.

〔方法並びに成績〕

We investigated whether *in vivo* introduction of synthetic double-stranded STAT3 decoy oligodeoxynucleotides (ODNs) can provide benefits for reducing organ injury and mortality in mice with cecal ligation and puncture (CLP)-induced polymicrobial sepsis. We found that STAT3 was rapidly activated in major end-organ tissues following CLP, which was accompanied by activation of the upstream kinase JAK2. Transfection of STAT3 decoy ODNs downregulated pro-inflammatory cytokine/chemokine overproduction in CLP mice. Moreover, STAT3 decoy ODN transfection significantly reduced the increases in tissue mRNAs and proteins of high mobility group box 1 (HMGB1) and strongly suppressed the excessive elevation in serum HMGB1 levels in CLP mice. Finally, STAT3 decoy ODN administration minimized the development of sepsis-driven major end-organ injury and led to a significant survival advantage in mice after CLP. Also, the STAT3 inhibitor stattic mimic the beneficial effects of STAT3 decoy ODN transfection on pro-inflammatory cytokine upregulation and organ injury in mice with CLP-induced sepsis.

〔総括〕

In conclusion, our present work provides evidence that STAT3 plays a critical role in the pathophysiology of sepsis. We also demonstrate that transfection of STAT3 decoy ODNs affords protection against the development of sepsis-driven major end-organ injury and leads to a prominent survival advantage in mice after CLP. While appreciating that several crucial issues, including safety and adverse effects, have to be addressed in further study, our results suggest that STAT3 suppression with the use of transcription decoy strategy may represent a novel and efficacious therapeutic option for sepsis treatment.