TNF-a Inhibits Toll-like Receptor 4 Expression on Monocytic Cells via Tristetraprolin During Cardiopulmonary Bypass

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摘要

Abstract

Toll-like receptor 4 (TLR4) plays a major role in regulating the innate immune response, which is related to postoperative complications. Although inflammatory capacity and TNF-alpha synthesis were altered on monocytes after cardiopulmonary bypass (CPB), whether the CPB and the CPB-induced TNF-alpha affect TLR4 expression on monocytes have not yet clarified. We speculate that the changing of TNF-alpha level during CPB may be involved in monocytic TLR4 expression. As previous report, our enzyme-linked immunosorbent assay showed that CPB elevated the plasma level of TNF-alpha, whereas off-pump cardiac surgery does not. Flow cytometry reported decreased levels of monocytic TLR4 in patients undergoing CPB but not undergoing off-pump cardiac surgery. To elucidate whether the CPB-induced TNF-alpha is related to TLR4 down-regulation, we used human monocytic THP-1 cells. Actinomycin D chase experiments demonstrated that TNF-alpha decreased TLR4 expression and TLR4 mRNA stability on THP-1. Confocal microscopy and real-time polymerase chain reaction showed that TNF-alpha induced intracellular tristetraprolin (TTP) expression. Transfection with TTP siRNA reversed the down-regulation of TLR4 in TNF-alpha-stimulated THP-1. Treatment with ERK1/2 inhibitor and SAPK/JNK inhibitor decreased TNF-alpha-induced TTP expression. Immunoprecipitation and Western blot analysis showed that the TNF-alpha-mediated activation of TTP might be inhibited by p38 mitogen-activated protein kinase inhibitor and by PD98059. We also demonstrated in clinical samples with confocal microscopy and flow cytometry that CPB led to an elevation of TTP in monocytes. In

conclusion, CPB and TNF-alpha decrease TLR4 expression on monocytes; TTP expression and mitogen-activated protein kinase-signaling pathways play critical roles in CPB- and TNF-alpha-mediated decreases of TLR4 on monocytes. Our results suggest that using TTP to control cytokine message decay rate may be a promising approach for controlling system inflammation and preventing post-CPB complications.