

Endotoxin Induces Toll-Like Receptor 4 Expression in Vascular Smooth Muscle Cells via NADPH Oxidase Activation and Mitogen-Activated Protein Kinase Signaling Pathways.

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摘要

Abstract

OBJECTIVE: Toll-like receptor 4 (TLR4) plays a major role mediating endotoxin-induced cellular inflammation and regulates vascular smooth muscle cell (VSMC) proliferation, which is related to atherogenesis and restenosis. This study was conducted to investigate the mechanisms involved in lipopolysaccharide (LPS)-induced TLR4 expression in VSMCs. **METHODS AND RESULTS:** Stimulation of human aortic smooth muscle cells (HASMCs) with LPS significantly increased TLR4 expression. The increase was regulated by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (including the activation of subunits p47(phox) and Rac1), which mediates the production of reactive oxygen species and the activation of intracellular mitogen-activated protein kinase signaling pathways. Treatment with polyethylene-glycol-conjugated superoxide dismutase, N-acetylcysteine (NAC), diphenylene iodonium (DPI), or apocynin significantly decreased LPS-induced TLR4 expression. An actinomycin D chase experiment showed that LPS increased the half-life of TLR4 mRNA. Inhibition of NADPH oxidase activity by DPI, apocynin, or NAC significantly decreased TLR4 mRNA stability, as did the knock-down of RAC1 gene expression by RNA interference. We also demonstrated in an animal model that LPS administration led to a significant elevation of balloon-injury-induced neointimal hyperplasia, and of TLR4 expression, in rabbit aorta. **CONCLUSIONS:** These findings suggest that NADPH oxidase activation, mRNA stabilization, and MAPK signaling pathways play critical roles in LPS-enhanced TLR4 expression in HASMCs, which contributes to vascular inflammation and cardiovascular disorders.