Sensitization of Human Aortic Endothelial Cells to Lipopolysaccharide via Regulation of Toll-Like Receptor 4 by Bacterial Fimbria-Dependent Invasion

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Abstract

Toll-like receptors (TLRs) are differentially up-regulated in response to microbial infection and chronic inflammatory diseases such as atherosclerosis. Epidemiological data support the idea that periodontal disease may be a risk factor for acceleration of atherosclerosis. Porphyromonas gingivalis, the etiological agent of periodontal disease, invades endothelium, has been detected in human atheromatous tissue, and accelerates atheroma formation in apolipoprotein E-/- mice with concurrent induction of TLRs in the aorta. As endothelial cells can present antigen via TLRs and play an important role in the development of atherosclerosis, we examined TLR expression in human aortic endothelial cells (HAEC) cultured with wild-type P. gingivalis, a fimbria-deficient mutant, and purified antigens. We observed increased TLR expression in HAEC infected with wild-type P. gingivalis by fluorescence-activated cell sorter, but not with noninvasive, fimbria-deficient mutant or purified P. gingivalis antigens. Following a wild-type P. gingivalis challenge, functional TLR2 and TLR4 activation was assessed by subsequent stimulation with TLR agonists Staphylococcus aureus lipoteichoic acid (SLTA; TLR2 ligand) and Escherichia coli lipopolysaccharide (LPS; TLR4 ligand). Unchallenged HAEC failed to elicit monocyte chemoattractant protein 1 (MCP-1) in response to LPS or SLTA but did so when cultured with wild-type P. gingivalis. P. gingivalis-induced TLR2 and -4 expression on HAEC functionally reacted to SLTA and E. coli LPS as measured by a further increase in MCP-1 production. Furthermore, MCP-1 expression elicited by E. coli LPS was inhibitable with TLR4-specific antibody and polymyxin B. These results indicate that invasive P. gingivalis stimulates TLR expression on the surface of endothelium and these primed cells respond to defined TLR-specific ligands.