Role for fimbriae and lysine-specific cysteine proteinase gingipain K in expression of interleukin-8 and monocyte chemoattractant protein in Porphyromonas gingivalis-infected endothelial cells.

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Abstract

Recent cross-sectional and prospective epidemiological studies have demonstrated an association between periodontal disease and atherosclerosis and human coronary heart disease. Previously, we have established that the periodontal pathogen Porphyromonas gingivalis is capable of invading aortic, heart, and human umbilical vein endothelial cells (HUVEC). Since atherosclerosis is a chronic inflammatory response initiated at the vascular wall, interactions of P. gingivalis with endothelial cells and the subsequent host cell response to infection may be important in the pathogenesis of atherosclerosis. In this study we examined the consequences of P. gingivalis infection of HUVEC on the expression of the chemokines interleukin-8 (IL-8) and monocyte chemotactic protein 1 (MCP-1). HUVEC were found to constitutively produce low levels of IL-8 and MCP-1. The addition of P. gingivalis fimbrillin-specific peptides, lipopolysaccharides (LPS), or heat-killed whole cell preparations to HUVEC stimulated modest IL-8 and MCP-1 responses. In contrast, coculture of HUVEC with live P. gingivalis strain A7436, 33277, or 381 abolished the IL-8 and MCP-1 responses. Inhibition of IL-8 and MCP-1 production was not dependent on bacterial adherence since similar results were obtained with the nonadherent P. gingivalis fimA mutant DPG3 or when P. gingivalis was preincubated with fimbrillin peptide antisera prior to the addition to HUVEC. Furthermore, treatment of P. gingivalis-infected HUVEC with cytochalsin D, which prevented P. gingivalis invasion, also abolished the constitutive IL-8 and MCP-1 responses. Treatment of HUVEC with E. coli LPS stimulated robust IL-8 and MCP-1 responses that were abolished when stimulated cells were cocultured with live P. gingivalis. Analysis of P. gingivalis-infected HUVEC cultures by an RNase protection assay revealed an increase in the IL-8 transcript relative to uninfected HUVEC. Pretreatment of P. gingivalis with protease inhibitors prior to the addition to HUVEC

prevented the inhibition of IL-8 and MCP-1 production in P. gingivalis-infected HUVEC, indicating that the inhibition was proteolytically mediated. Coculture of HUVEC with a P. gingivalis mutant deficient in lysine-specific cysteine proteinase (gingipain K [Kgp]) resulted in an increase in both IL-8 transcription and protein expression relative to that observed in HUVEC cocultured with the P. gingivalis wild-type strain. These results indicate that P. gingivalis can temporally modulate the chemokine response in endothelial cells through both fimbriae and gingipain-mediated mechanisms.