Histone-like DNA binding protein of *Streptococcus intermedius* induces the expression of pro-inflammatory cytokines in human monocytes via activation of ERK1/2 and JNK pathways

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**Objectives:** *Streptococcus intermedius* is an oral commensal associated with endodontic origin abscess and periodontal abscess. It can also cause serious, deep-seated purulent infection in major organs, such as the brain and liver. Histone-like DNA binding protein (HLP) is a nucleoid-associated protein in the bacterial chromatin. Due to its DNA and mRNA binding capacity, HLP has been mainly investigated as an accessory architectural factor in a variety of bacterial cellular processes. The aim of this study was to investigate the stimulatory properties of histone-like DNA binding protein of *S. intermedius* (*Si*-HLP) and the mechanisms of pro-inflammatory cytokine inductions in human monocytes by its stimulation.

**Materials and methods:** The recombinant *Si*-HLP (r*Si*-HLP) was used to stimulate human monocytic cells, the THP-1 cells. Pro-inflammatory cytokine secretion in the cell supernatants was measured by enzyme-linked immunosorbent assay (ELISA). The mRNA expression of the cytokines was determined by reverse transcription-PCR (RT-PCR). r*Si*-HLP-stimulated signaling pathway was examined using specific inhibitors and the phosphorylation of the MAPKs was confirmed by Western blotting analysis.

**Results:** r*Si*-HLP stimulation-induced production of pro-inflammatory cytokines (IL-8, IL-1β and TNF-α) occurred in a time- and dose-dependent manner. In contrast with the heat-stable activity of DNA binding, the cytokine induction activity of r*Si*-HLP was heat-unstable. In subsequent studies, r*Si*-HLP acted cooperatively with lipoteichoic acid, the synthetic Toll-like receptor 2 agonist, Pam3CSK4, and the cytosolic nucleotide-binding oligomerization domain 2 receptor agonist, muramylidipeptide (MDP). Furthermore, Western blot and blocking assays with specific inhibitors showed that r*Si*-HLP stimulation induced the activation of cell signal transduction pathways, extracellular signal-regulated kinase 1/2 (ERK1/2) and c-Jun N-terminal kinase (JNK).

**Conclusion:** In addition to its physiological role in bacterial growth through DNA binding, these results indicate that *Si*-HLP can trigger a cascade of events that induce pro-inflammatory responses via ERK1/2 and JNK signal pathways, and suggest that bacterial HLP may contribute to the activation of host innate immunity during bacterial infection.