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Systems biology unravels a novel pathogenic mechanism of heterogeneous *P. gingivalis* lipid A structures in chronic periodontitis

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BACK GROUND : *Porphyromonas gingivalis* lipopolysaccharide (PgLPS) is a crucial virulence factor strongly associated with chronic periodontitis. *P. gingivalis* exploits its ability to shift between tetra-acylated ($LPS_{1435/1449}$) and penta-acylated (LPS_{1690}) lipid A isoforms during periodontitis.

OBJECTIVES : Present study was designed to comprehensively investigate the modulation of immuno-inflammatory activity, lipid perioxidation and apoptotic pathways in human gingival fibroblasts (HGFs) by PgLPS isoforms.

EXPERIMENTAL METHODS : Primary HGFs were treated with P. *gingivalis* $LPS_{1435/1449}$ and LPS_{1690} in dose-dependent and time-dependent experiments. Involvement of TLRs and signal transduction pathways were examined using blocking assays. Down-stream markers were examined by qPCR, ELISA and Western blot. Next, systems biology tools i.e. proteomics, metabolomics, transcriptomic and bioinformatics were used to unravel the global protein and gene expression of HGF for PgLPS isoforms. Generic and specific biomarkers were cataloged using bioinformatics tools. RNA harvested from HGFs was subjected to transcriptomic analysis using gene-arrays in Toll-Like receptor, lipid peroxidation and apoptosis pathways. Identified biomarkers were further validated using Western blot and qPCR.

RESULTS : Heterogeneous lipid A structures of *P. gingivalis* showed strikingly different immuno-inflammatory activity. $PgLPS_{1690}$ induced pro-inflammatory cytokines IL-6, IL-8, TNF-α, GM-CSF. In contrast, $PgLPS_{1435/1449}$ induced anti-inflammatory molecules (SOCS box) and reduced lipid peroxidation pathway molecules such as perilipin and superoxide dismutase. $PgLPS_{1690}$ activated apoptosis (Bax-Caspase) related pathway whereas $PgLPS_{1435/1449}$ inhibited. Interestingly, we discovered that PgLPS isoforms utilize different mechanisms (TLRs, signal transduction pathways) for the modulation of host innate immune system which could account for aforementioned observation.

CONCLUSION : We have for the first time unraveled the molecular mechanism behind heterogeneous PgLPS isoforms which explain the ability of *P. gingivalis* to disguise host immune response to survive and proliferate in gingival tissues as a periodontal pathogen. Novel pathogenic mechanism described herein will certainly lay a new foundation to develop novel strategies for periodontal diseases (HKU766909M to LJJ).