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Intracellular NOD2 activation promotes maturation and antigen-presenting functions of dendritic cells exposed to *Porphyromonas gingivalis* lipopolysaccharide.

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Abstract

Objective: This study aimed to study the roles of Muramyl Dipeptide (MDP) which is an agonist of NOD2 in Dendritic Cells (DCs) exposed to *Porphyromonas gingivalis* lipopolysaccharide (*P. gingivalis*-LPS) on maturation and antigen-presenting functions of DCs to provide experimental evidences to explore the possible mechanism of DCs in periodontitis.

Methods: Flow cytometry was used to detect CD11c, MHC-II, CD80, CD86, and CD40 expression on DCs and ELISA was used to detect IL-12, IFN-γ, IL-10, and IL-13 secreted by DCs which were stimulated by MDP and *P. gingivalis*-LPS, respectively or in synergism. RT-PCR analysis was used to detect NOD2, TLR2, and TLR4 mRNA expression in DCs stimulated by MDP and *P. gingivalis*-LPS, respectively or in synergism. CCK8 was used to assess CD4+ T cells proliferation after co-cultured with DCs stimulated by MDP and *P. gingivalis*-LPS, respectively or in synergism and ELISA was used to detect IL-2, IFN-γ, IL-10 and IL-13 secreted by these T cells.

Results: MDP had weak ability to stimulate DCs maturation but MDP could promote DCs maturation stimulated by *P. gingivalis*-LPS. MDP was NOD2 agonist to DCs and *P. gingivalis*- LPS was TLR2 but not TLR4 agonist to DCs. MDP could facilitate TLR2 mRNA expression in DCs exposed to *P. gingivalis*-LPS. The ability of MDP to promote DCs secreting cytokines was far below *P. gingivalis*-LPS but MDP could promote the functions of Th2 cell-promoting DCs induced by *P. gingivalis*-LPS. MDP could promote $CD4^+$T cells proliferation primed by DCs exposed to *P. gingivalis*-LPS and elevate the ability of DCs exposed to *P. gingivalis*-LPS to prime Th0 cells to Th2 cells.

Conclusion: Intracellular NOD2 in DCs could be activated by MDP and this activation could promote maturation and the ability to prime Th0 cells to Th2 cells of DCs exposed to *P. gingivalis*-LPS.

Keywords: Muramyl dipeptide, *P. gingivalis*-LPS, Dendritic cells, Maturation, Antigen-presenting.

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Introduction

Dendritic Cells (DCs) are widely distributed in tissues and organs and they are the body's most efficient Antigen-Presenting Cells (APCs) [1]. Immature DCs uptake antigens and mature DCs present antigens to naive T-lymphocytes, then stimulate naive T cells to differentiate to be effector T cells [2], thus, DCs are important key mediators between innate and acquired immune responses [3]. Priming DCs with microbial compounds up-regulates the expression of costimulatory molecules and the production of proinflammatory cytokines, which drives T-helper (Th) cells to differentiate to Th1 or Th2 cells [4]. The first step of the process is that DCs identify various antigenic materials which are called Pathogen-Associated Molecular Patterns (PAMP) by Pattern Recognition Receptors (PRRs) which are expressed either on the surface or in the cytoplasm of DCs. Thus, PRRs and their ligands have important roles in DCs maturation and antigen-presenting function.

Porphyromonas gingivalis (*P. gingivalis*) is a kind of gram-negative anaerobic rod-shaped bacteria and it is a pathogenic microorganism in the development of Chronic Periodontitis (CP) [5]. The pathogenic components of *P. gingivalis* include: Lipopolysaccharide (LPS), capsular polysaccharide, fimbrial proteins, and gingipains [6]. *P. gingivalis*-LPS is one of the main pathogenic factors to periodontitis and *P. gingivalis*-LPS can elicit various types of immune and inflammatory responses in periodontitis [7]. It is generally accepted that LPS is Toll-Like Receptors (TLR) 4 ligands [8], while there are also many studies declared that different with *E. coli*-LPS which majorly activated TLR4, *P. gingivalis*-LPS majorly activated TLR2 [9].

Besides TLRs, there is also another type of important signal transduction PRRs existing in DCs cytoplasm which also play