MOLECULAR MECHANISMS OF *PORPHYROMONAS GINGIVALIS* LIPOPOLYSACCHARIDE IN PERIODONTITIS PATHOGENESIS

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ABSTRACT

Introduction: Periodontitis is a chronic inflammatory disease that leads to progressive destruction of periodontal tissues, ultimately causing tooth loss. The Gram-negative bacterium *Porphyromonas gingivalis* (*P. gingivalis*) is a key pathogen in periodontitis, with lipopolysaccharide (LPS) playing a major role in immune modulation and inflammatory responses. This review examines the molecular mechanisms by which *P. gingivalis* LPS contributes to periodontitis pathogenesis, focusing on immune response, epigenetic modifications, and hypoxia-induced inflammation. **Methods:** A literature search was conducted using PubMed and Google Scholar to identify studies published in the last 10 years. The search was performed using the keywords 'Porphyromonas gingivalis,' 'lipopolysaccharide,' and 'periodontitis.' Articles were selected based on language (English or Indonesian) and full-text availability. **Results and Discussion:** *P. gingivalis* LPS activates Toll-like receptor 4 (TLR4), leading to pro-inflammatory macrophage polarization and cytokine release. It also induces epigenetic modifications, such as DNA methylation reduction and histone acetylation, which sustain inflammation. Additionally, hypoxia amplifies caspase-1 activation, worsening periodontal tissue destruction. **Conclusion:** The involvement of *P. gingivalis* LPS in periodontitis suggests that immune dysregulation, epigenetic modifications, and hypoxia-induced inflammation are key drivers of the disease. Targeting LPS-TLR4 interactions and inflammatory pathways may offer new therapeutic strategies for managing periodontitis.

Keywords: Lipopolysaccharide, Periodontitis, *Porphyromonas gingivalis*

Introduction

Periodontitis is a chronic multifactorial inflammatory disease characterized by progressive destruction of the teeth-supporting apparatus, resulting in tooth mobility and eventual loss.[1] In Indonesia, the 2018 Basic Health Research (Riskesdas) report revealed a notably high prevalence of periodontitis, affecting 74.1% of the population.[2] The development of periodontal dysbiosis occurs over a broadened timeframe, which slowly turns the symbiotic association of the host and the microbe to pathogenic form.[3] The subgingival biofilm of specific gram-negative, anaerobic microorganisms, termed red complex *P. gingivalis*, *Tannerella forsythia*, and *Treponema denticola* encompasses the most important pathogens in adult periodontal disease.[4]

Porphyromonas gingivalis is a Gram-negative bacterium recognized as an important etiological agent of human chronic periodontitis.[5] *P. gingivalis* is one of the red complex bacteria that has been shown to have the strongest association with the severity of gingival conditions.[6] This bacterium-induced chronic inflammatory disease, affecting a large proportion of the population, is characterized by resorption of alveolar bone surrounding the tooth root surface, resulting in the eventual exfoliation of the teeth. A major constituent of the outer membrane of *P. gingivalis* is LPS, which plays a critical role in mediating inflammation and inducing cells to secrete pro-inflammatory cytokines and an important virulence factor of gram- negative bacteria.

This review aims to summarize the molecular mechanisms by which *P. gingivalis* LPS contributes to the pathogenesis of periodontitis, focusing on the key signaling pathways involved and the resulting inflammatory responses. By understanding how *P. gingivalis* LPS triggers and modulates inflammation, we can gain insights into the molecular interactions that drive periodontal disease progression, ultimately guiding the development of targeted therapeutic strategies to mitigate the inflammatory effects and control disease advancement.

Methods

A literature search was performed in several electronic databases, including PubMed and Google Scholar, to identify studies examining the molecular mechanisms of *P. gingivalis* LPS infection. Publications were selected based on the following criteria: (1) articles written in English or Indonesian, (2) use of the keywords *'Porphyromonas gingivalis*,' 'lipopolysaccharide,' and 'periodontitis,' (3) studies published within the last 10 years, and (4) only full-text articles were included. Relevant information from each study was gathered and summarized.

Results

Table 1. Summary of Selected Studies on *P. gingivalis* LPS in Periodontitis

Authors, Years	Type of Research	Title	Related Findings
Veloso et al. (2022)	In Vitro Study	Lipopolysaccharide from *Porphyromonas gingivalis*, but Not from *Porphyromonas endodontalis*, Induces Macrophage M1 Profile	LPS from *P. gingivalis* induces M1 macrophage profile, whereas *P. endodontalis* LPS does not trigger a significant inflammatory response.
Akkaoui et al. (2020)	In Vitro Study	Contribution of *Porphyromonas gingivalis* lipopolysaccharide to experimental periodontitis in relation to aging	*P. gingivalis* LPS enhances osteoclast differentiation in young mice but has a weaker effect in aged mice, suggesting age-related immune modulation.
Diomede et al. (2017)	In Vitro Study	*Porphyromonas gingivalis* lipopolysaccharide stimulation in human periodontal ligament stem cells: Role of epigenetic modifications to the inflammation	LPS from *P. gingivalis* alters DNA methylation and histone acetylation, increasing NF-κB-mediated inflammation in periodontal ligament stem cells.
Li et al. (2020)	In Vitro Study	The Effect of *Porphyromonas gingivalis* Lipopolysaccharide on the Pyroptosis of Gingival Fibroblasts	*P. gingivalis* LPS induces caspase-1 activation, leading to pyroptosis in human gingival fibroblasts, which exacerbates tissue damage.
Cheng et al. (2017)	In Vitro Study	Porphyromonas gingivalis-Derived Lipopolysaccharide Combines Hypoxia to Induce Caspase-1 Activation in Periodontitis	Hypoxia increases caspase-1 activation and IL-1β secretion, worsening inflammation in periodontitis when combined with *P. gingivalis* LPS.

The role of *P. gingivalis* LPS in periodontitis has been extensively studied due to its involvement in immune modulation, inflammation, and tissue destruction.[7,8] As a major virulence factor, *P. gingivalis* LPS interacts with TLR4, triggering immune responses that drive disease progression. This interaction promotes macrophage polarization toward the M1 pro-inflammatory phenotype, leading to increased secretion of inflammatory cytokines. The resulting inflammatory environment contributes to connective tissue breakdown and alveolar bone resorption, both hallmark features of periodontitis.

Furthermore, *P. gingivalis* LPS plays a crucial role in osteoclastogenesis, with its effects varying by age.[9,10] Studies suggest that younger individuals, who exhibit higher TLR4 expression, experience a more pronounced osteoclastogenic response, whereas older individuals show reduced TLR4-mediated immune activity, resulting in a chronic but less aggressive disease progression. In addition to immune modulation, *P. gingivalis* LPS has been implicated in epigenetic modifications that prolong inflammatory responses. Research indicates that LPS reduces DNA methylation while increasing histone acetylation, leading to sustained activation of inflammatory pathways. This mechanism ensures that even after the initial bacterial challenge subsides, inflammatory genes remain active, perpetuating periodontal tissue destruction.

Beyond its role in inflammation and epigenetic alterations, *P. gingivalis* LPS also induces pyroptosis, a form of programmed cell death, in gingival fibroblasts.[8,11] Pyroptosis, characterized by caspase-1 activation and cell membrane rupture, leads to the release of pro-inflammatory mediators, further exacerbating periodontal damage. Additionally, *P. gingivalis* thrives in hypoxic environments, which intensify its pathogenic effects. Studies have shown that hypoxia in periodontal pockets enhances LPS-induced inflammation by increasing caspase-1 activation and interleukin-1β (IL-1β) maturation, accelerating tissue destruction. This suggests that low oxygen levels amplify the virulence of *P. gingivalis* LPS, making periodontitis more aggressive and difficult to control.

Taken together, these findings underscore the multifaceted role of *P. gingivalis* LPS in periodontitis, encompassing immune evasion, inflammatory modulation, epigenetic alterations, and cell death induction.[9,10] Future therapeutic approaches targeting LPS-TLR4 interactions, pyroptosis pathways, and hypoxia-induced inflammatory responses may offer promising strategies for managing periodontitis progression.

Discussion

The multifaceted role of *P. gingivalis* LPS in periodontitis progression involves immune modulation, epigenetic regulation, and inflammatory tissue destruction.[7,9] One key finding is that *P. gingivalis* LPS interacts with TLR4, driving macrophage polarization toward a pro-inflammatory M1 phenotype and promoting immune dysregulation. However, the immune response to LPS appears to be age-dependent. Younger individuals exhibit higher TLR4 activation, leading to more aggressive bone resorption, whereas older individuals experience reduced immune activation, resulting in a chronic but less intense inflammatory response. This suggests that TLR4 expression declines with age, altering the immune system's ability to effectively combat periodontal pathogens.

Beyond immune modulation, *P. gingivalis* LPS induces epigenetic changes that sustain inflammatory gene activation.[10] Research has shown that LPS reduces DNA methyltransferase

1 (DNMT1) expression while increasing histone acetyltransferase p300 levels in human periodontal ligament stem cells (hPDLSCs). These alterations activate nuclear factor kappa B (NF-κB), a key transcription factor in inflammatory signaling, thereby prolonging inflammation in periodontal tissues. Additionally, epigenetic mechanisms, including DNA methylation and histone modifications, play a crucial role in immune regulation and inflammation.[12] Environmental factors, such as bacterial pathogens, can induce these modifications, further exacerbating periodontal disease progression.[13]

In addition to immune and epigenetic regulation, *P. gingivalis* LPS has been shown to trigger pyroptosis in gingival fibroblasts.[11] This form of programmed cell death, mediated by caspase-1 activation, leads to cell rupture and the release of inflammatory mediators, exacerbating tissue destruction.[8] Another critical factor influencing disease severity is hypoxia within periodontal pockets. Hypoxic conditions amplify the inflammatory effects of LPS by enhancing caspase-1 activation and IL-1β maturation, accelerating periodontal tissue breakdown. These findings suggest that hypoxia creates an environment that enhances *P. gingivalis* pathogenicity, making periodontitis more severe and difficult to manage.

Given these insights, incorporating epigenetic regulatory mechanisms into periodontal treatment strategies could provide a novel therapeutic approach. Targeting LPS-TLR4 interactions, modulating DNA methylation patterns, and addressing hypoxia-induced inflammation may offer new strategies for controlling periodontitis progression.

Conclusion

P. gingivalis LPS plays a key role in periodontitis by triggering immune dysregulation, epigenetic changes, and inflammatory tissue destruction. Its interaction with TLR4 promotes inflammation, with age-related differences affecting disease severity. Epigenetic modifications sustain inflammatory responses, while pyroptosis and hypoxia further amplify tissue damage. These findings suggest that targeting LPS-TLR4 interactions, epigenetic regulation, and hypoxia-induced inflammation could offer new strategies for managing periodontitis.

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