Review

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# Virulence Mechanisms of *Porphyromonas gingivalis*: Gingipains and Beyond– A review

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## ABSTRACT

*Porphyromonas gingivalis* is a key pathogen strongly implicated in the onset and progression of periodontitis. The virulence of this bacterium consists of a number of modern methods, and thus it protects itself from the immunity of the organism it infects, causing damage to tissues and colonizing the oral cavity. Gingipains, a virulence factors for these bacteria, include cysteine enzymes RgpA, RgpB, and Kgp. They degrade proteins of the host organism, enabling the bacteria to easily escape the host's immune defense mechanisms. Other virulence factors include fimbriae, capsule, outer membrane vesicles and lipopolysaccharides, Which enable bacteria to adhere to, invade, and destroy living tissue. Periodontal bacteria cause gingivitis because of their ability to disrupt the bacterial balance. These bacteria can exist and adapt within living cells, thereby causing disease. Understanding their virulence strategies and mechanisms is essential to developing treatments to eliminate or control diseases caused by gingival bacteria. This review will address the virulence factors of periodontal bacteria, their mechanism of action, and the damage they cause to oral tissues during and after infection.x

**Keywords**: cysteine enzymes; gingivitis; gingival bacteria; oral microbiota ;virulence factors

## INTRODUCTION

Periodontal bacteria possess many virulence factors that enable them to exist, invade, and influence the host's immune defense mechanisms, leading to chronic inflammation and disruption



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and destruction of host tissues[1,2]. Periodontal bacteria are present in the oral cavity and cause gingivitis. It is non-motile, Gram-negative, and can't live without air [3]. Periodontal bacteria infect the epithelial cells in the gums and can survive even when antibiotics are used. The bacteria degrade collagen by secreting collagenase enzymes. It is noted that patients suffering from periodontitis have high levels of specific antibodies[4]. Gingivitis is an inflammation that affects the tissues surrounding the tooth in the early stages, and then leads to bleeding gums and tooth loss worldwide [5]. Gingivitis is caused by the presence of a layer of plaque biofilm, which is a collection of gingival bacteria, which leading to inflammation of the tissues surrounding the teeth due to failure to use treatment[6].

Treatment for gingivitis includes oral hygiene. Teeth should be cleaned daily, and a visit to the dentist should be made, and in some cases, antibiotics are used, and surgery may be required . Treatment methods also include quitting smoking and following a diet that improves gum health. [7,8].

## Gingipains: The Central Virulence Tool

*P. gingivalis* possesses a number of virulence factors, including cysteine proteases called gingipains[9]. These enzymes RgpA, RgpB, and Kgp are involved in nutrient acquisition, immune evasion, and tissue breakdown. They degrade host proteins including cytokines, immunoglobulins, and extracellular matrix components, thus facilitating bacterial survival and dissemination[10] (figure 1).

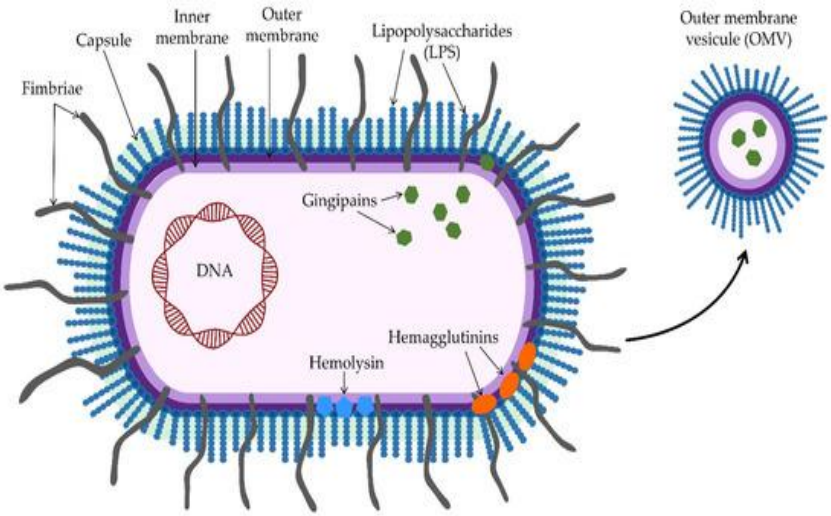

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**Figure 1.** *P. gingivalis* and cysteine proteases[11].

## Fimbriae and Adhesions

Gingival bacteria possess adhesion proteins, including: fimbriae and gingipain hemagglutinin which been engaged as adhesions that operate colonization of epithelium lining the gingival tissues [12]. Fimbriae such as FimA and Mfa1 are essential for bacterial adhesion to host tissues and other microbes. They promote colonization, biofilm formation, and interactions with immune cells, modulating host responses[13]. Fimbriae play a vital role in facilitating the interaction of bacteria with host tissues and promoting their invasion. P. gingivalis produces two structurally distinct types of fimbriae including long and short on its surface, both of which are implicated in the progression of periodontitis. Long fimbriae are categorized into six variants (types I to V and Ib), according to the genetic variation within the fimA gene that encodes the FimA protein subunit. Research has shown that clones expressing type II fimA possess notably enhanced abilities for adhesion and invasion compared to other fimA types. Both long and short fimbriae have been linked to the stimulation of proinflammatory cytokines, including IL-1α, IL-1β, IL-6, and TNF-α, contributing to alveolar bone degradation. While the genetic diversity of short fimbriae remains insufficiently characterized, different strains of P. gingivalis have been found to carry distinct short fimbrial proteins, suggesting that such variations may impact the pathogenesis of periodontal disease[14](figure 2)

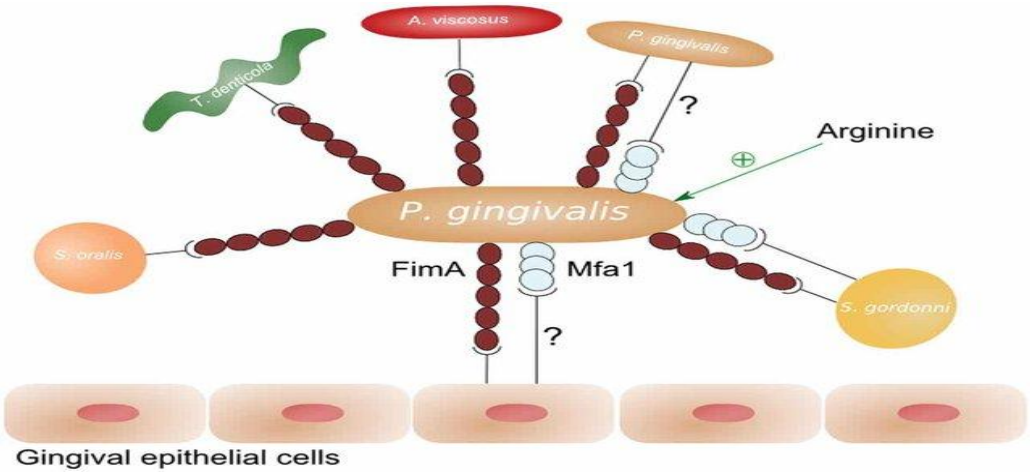


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**Figure 2**: The fimbriae of *P. gingivalis*, specifically FimA and Mfa1, are known to interact with epithelial cells as well as other microbial species. However, some of these interactions or their exact effects remain uncertain, as indicated by question marks in relevant models[15].

## Capsule and Immune Evasion

The capsule of *P. gingivalis* helps it evade phagocytosis and inhibits complement activation. It reduces recognition by immune cells and contributes to persistence in the host[16].The capsule of this bacteria significantly contributes to its ability to escape detection by the host's immune system, enhances its intracellular persistence, and intensifies its pathogenic potential. Therefore, it is considered a key factor in the organism's virulence[17]. The role of the capsule is to protect the bacterial cell and prevent it from being detected by immune cells by hiding the surface antigens, which reduces the possibility of immune activation[16]. The capsule-containing bacterial strains activate the inflammatory response less than the non-capsulated bacterial cells, which may help these capsule-containing bacteria to survive, invade and destroy the host tissues. [18].

## Lipopolysaccharide (LPS) and Immune Modulation

The lipopolysaccharide in gingival bacteria has structural forms of lipid A that selectively activate TLR2 and TLR4 receptors. This signal disrupts the normal immune mechanism and perpetuates chronic inflammation[19]. Periodontal bacteria produce lipopolysaccharide, which plays a role in shaping the host immune response through the development of gingivitis. Gingival bacteria form lipopolysaccharide-rich outer membrane vesicles that interact with the host's oral tissues and alter the activity of immune cells. In spite of lipopolysaccharide inducing inflammation through TLR4 receptors, it also has immunoregulatory functions that may affect both harmful and protective pathways within host tissues. [20].

One of the mechanisms used by gingival bacteria to invade host tissues is to secrete protein enzymes that destroy intercellular adhesion molecules and components of the extracellular matrix, which leads to weakening of the mucous membrane and enables bacteria to enter the tissues. Another mechanism of invasion is the process of transcytosis, through which the bacteria enter the epithelial cells and move to another cell, leading to tissue penetration. Furthermore, macrophages engulf the gingival bacteria and transfer them into the bloodstream. Finally, the

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gingival bacteria have the ability to bind to the *Candida albicans* fungus, which helps them invade the mucosal tissues, enabling them to reach deeper layers[21].

## Outer Membrane Vesicles (OMVs)

Gingival bacteria produce outer membrane vesicles rich in virulence components, including: gingipains, DNA, and RNA. These vesicles transport toxins and enzymes not only to nearby host cells at the infection site but also to distant tissues, leading to enhanced pathogenic effects on the host[22]. Outer membrane vesicles have the ability to initiate various signaling pathways within host cells, including MAPK and NF-κB, which in turn promote the release of pro-inflammatory cytokines[23]. Also, outer membrane vesicles can activate the NLRP3 inflammasome, participating in both peripheral and central inflammatory responses, including neuroinflammationThese vesicles can be taken up by host cells, enabling the direct delivery of their molecular contents and modulating key intracellular functions[24] (as shown in the figure3).

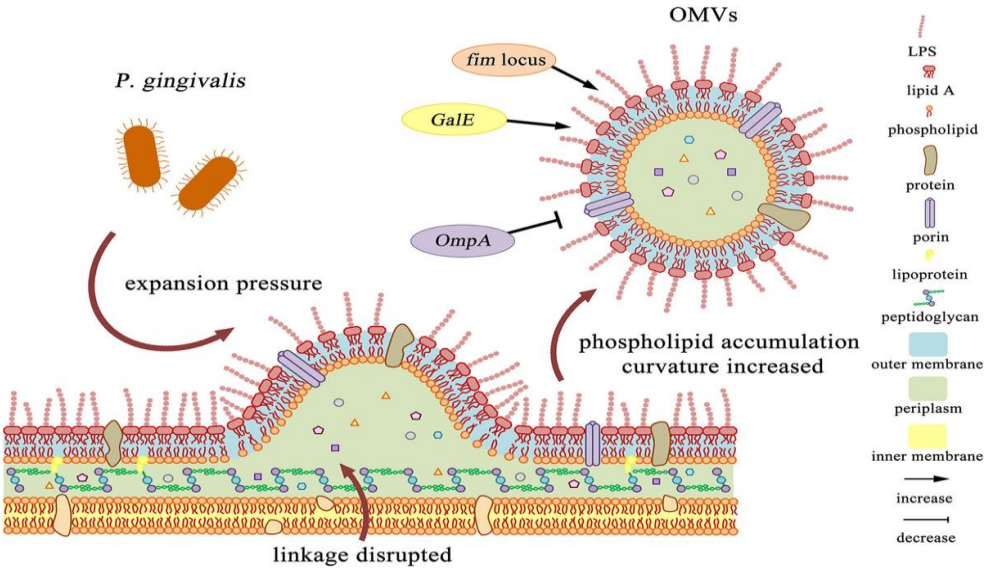

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**Figure 3:** The formation of OMVs begins after separation of the outer membrane from the cell wall. Phospholipids begin to accumulate in the outer leaflet of the membrane, generating expansion pressure that promotes further enrichment of outer membrane components. As the connection between the peptidoglycan layer and the outer membrane weakens, vesicle budding occurs, resulting in the release of *P. gingivalis* OMVs. Genetic regulation also influences OMV production. Mutations in the fim locus and GalE gene significantly reduce or eliminate OMV release, whereas disruption of the OmpA gene leads to overproduction of OMVs in *P. gingivalis*[22].

## Cross-talk with Host Immune Cells

*P. gingivalis* employs multiple strategies to modulate the host immune system. It influences macrophage behavior by altering cytokine expression profiles—enhancing the production of IL-6 and G-CSF, while suppressing cytokines such as RANTES and IL-1α, especially when macrophages are exposed to live bacteria rather than isolated bacterial components[25]. Furthermore, *P. gingivalis* interferes with phagolysosome maturation through signaling pathways involving C5aR1–TLR2 and CR3–ERK, leading to a reduction in IL-12 production and supporting intracellular bacterial survival[26]. In addition to innate immune evasion, the pathogen also disrupts adaptive immunity by downregulating IL-2 and IFN-γ secretion and promoting regulatory T cell (Treg) pathways, ultimately dampening T and B cell responses and facilitating persistent infection[27](figure 4).

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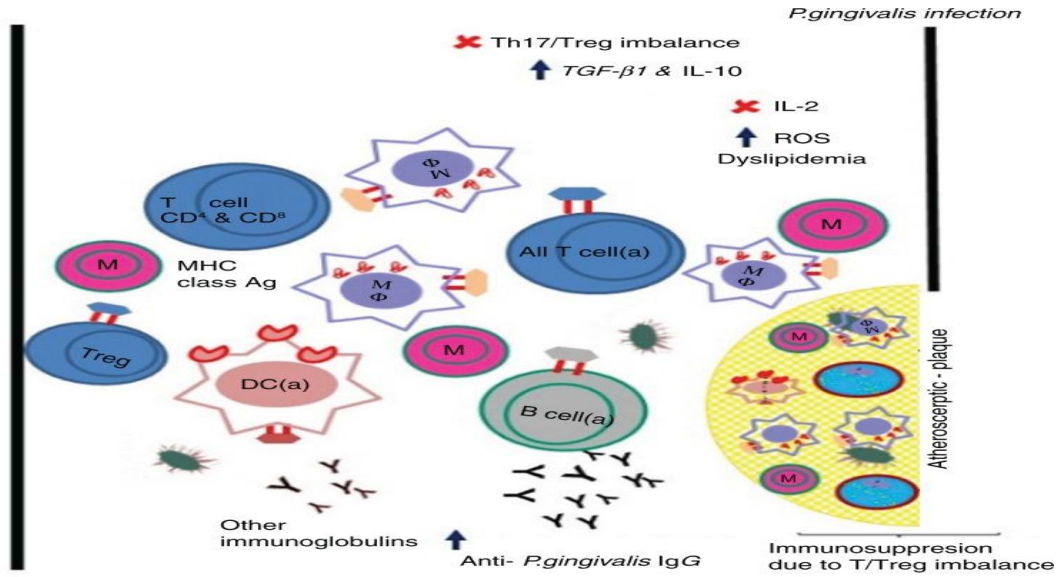


**Figure 4:** *P. gingivalis* has been implicated in the development of atherosclerosis through its ability to suppress adaptive immune responses. In the illustrated model, an open blood vessel is depicted containing an atherosclerotic plaque. Both the vessel and the plaque include a variety of immune cells both naïve and activated forms some expressing MHC class molecules and immunoglobulins. Foam cells are localized specifically within the plaque area. Under normal conditions, cytokine levels are balanced among immune cell populations. The immune cell types shown include naïve monocytes (M), activated macrophages (MF), naïve and activated T cells, activated dendritic cells (DC), and activated B cells. Functional antibodies are highlighted in pink-bordered structures, while non-functional ones are depicted in black. Elevated levels of *P. gingivalis* specific IgG antibodies in serum suggest the active involvement of the host's adaptive and humoral immune systems in response to this pathogen[27].

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### Interaction with Other Oral Microbiota

*P. gingivalis* forms cooperative interactions with other oral microorganisms, including *Fusobacterium nucleatum* and *Treponema denticola*, which support the development and stability of multispecies biofilms[28,29]. These synergistic relationships contribute to microbial imbalance in the oral cavity, driving the transition from a healthy to a dysbiotic microbial community commonly associated with periodontal disease[30].

## CONCLUSION

Gaining a deeper understanding of the diverse virulence mechanisms employed by *P. gingivalis* particularly its gingipain proteases, offers valuable perspectives on the development of periodontal disease. Targeting these factors in future therapeutic approaches could help interrupt disease progression and promote the reestablishment of oral health.Central Role of Gingipains: The review underscores that gingipains (RgpA, RgpB, Kgp) are the principal virulence factors of Porphyromonas gingivalis. These proteases are instrumental in breaking down host proteins, aiding immune evasion, and facilitating tissue destruction.Multiple Virulence Strategies: Beyond gingipains, P. gingivalis employs a range of mechanisms—fimbriae, capsule, outer membrane vesicles (OMVs), and lipopolysaccharides—to adhere to, invade, and damage host tissues.Immune System Modulation: The bacterium manipulates host immune responses at multiple levels. It skews cytokine production by macrophages and impairs both innate and adaptive immune defenses, which enables persistent infection and chronic inflammation. Host-Microbiome Interactions: The review highlights that P. gingivalis interacts not only with the host but also with other oral bacteria, contributing to the overall pathogenicity and complexity of periodontal disease. However, specific effects of these interactions require further clarification.

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## Conflict of interests

There are non-conflicts of interest.

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