Porphyromonas Gingivalis and Systemic Diseases

Subjects: Pathology
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The relationship between periodontitis and systemic diseases, notably including atherosclerosis and diabetes, has been studied for several years. *Porphyromonas gingivalis*, a prominent component of oral microorganism communities, is the main pathogen that causes periodontitis. We comprehensively summarize the adverse effects of *Porphyromonas gingivalis* on multiple systems and a variety of diseases, from extensively studied fields (cardiovascular diseases, cancer, adverse pregnancy outcomes, etc.) to emerging areas (Alzheimer's Disease, nonalcoholic fatty liver disease, depression, etc.). Although a few results remain controversial, it is now evident that *Porphyromonas gingivalis* should be regarded as a modifiable factor for several diseases.

Keywords: Porphyromonas gingivalis ; Systemic diseases ; Atherosclerotic cardiovascular diseases ; Oral squamous cell carcinoma ; Alzheimer’s Disease ; Diabetes ; periodontitis

1. Characteristics of *Porphyromonas gingivalis (P. gingivalis)*

P. gingivalis, one of over 700 bacterial species in the oral cavity, is a Gram-negative, anaerobic, rod-shaped bacteria that forms black colonies on blood agar and requires the presence of heme or hemin and vitamin K in its growth milieu. It is a successful colonizer of the oral epitheliumand an important component of subgingival microbiomes[1]. *P. gingivalis*is responsible for the chronic form of periodontitis, as it can remodel the commensal bacterial community to promote a state of dysbiosis[2]. Throughout evolution, it has developed unique and intricate mechanisms, such as the alteration of signaling pathways of inflammation, the complement system, the cell cycle, and apoptosis, and the interaction with various host receptors, thereby engineering its environment or modifying the host’s immune response to modulate the entire ecosystem and to persist in host tissues[3]. The survival strategies and pathogenicity of *P. gingivalis* largely depend on its diverse virulence factors, including its own structural components (lipopolysaccharide, fimbriae, heat shock proteins, etc.) and secretory components (gingipains and outer membrane vesicles).

Fimbriae are crucial for enabling *P. gingivalis* to specifically bind to eukaryotic cells and other species of bacteria to enhance bacterial motility, biofilm formation, and bacterial invasion of the cells [4]. It can also activate various host cells and subvert host immune clearance[4]. *P. gingivalis* lipopolysaccharide (LPS) can trigger the innate immune response via activation of Toll-like receptors (TLRs)[5]. The lipid A component of *P. gingivalis* LPS exhibits two predominant variations of acylation that are attributed to different strains and microenvironmental conditions: the penta-acylated LPS activates TLR4, while tetra-acylated LPS acts as a TLR4 antagonist and TLR2 agonist[5]. The heat shock protein 60 (HSP60) component of *P. gingivalis* is remarkably immunogenic and plays a critical role in *P. gingivalis*-induced autoimmune diseases[6]. Gingipains, which consist of lysine-gingipain (Kgp) and arginine-gingipain (Rgp), have multiple impacts on both innate and acquired immunity. These enzymes play essential roles in host colonization, host defense deactivation, tissue destruction, and nutrient acquisition[7]. Outer membrane vesicles (OMVs) from *P. gingivalis* are enriched in major virulence mediators, such as gingipains, LPS, and the capsule, and participate in biofilm development, host interaction, colonization, and immune defense evasion[8]. Moreover, its characteristic features, such as concentrated gingipains, together with its ability to travel to distant sites, might participate in *P. gingivalis*-associated systemic disorders[9].

P. gingivalis in local periodontal tissue can enter the vasculature through ulcerated epithelium[10] and lymph vessels[11] shortly after everyday activities, such as brushing and chewing, along with dental procedures. Some studies have indicated that *P. gingivalis* can survive in other organs besides the oral cavity. Viable *P. gingivalis* has been detected in human atherosclerotic plaque tissues[12] and mouse lungs[13] through tissue homogenates that were incubated with cells or cultured directly on blood agar plates. Cellular experiments have also provided evidence for the survival of *P. gingivalis* in some cells. For example, live *P. gingivalis* has been isolated from human aortic endothelial cells[14], human pancreatic tumor cells[15], and human myeloid dendritic cells[16]. All of the properties described above confer this species with the ability to invade distant tissues, where it is then involved in the onset and/or progression of systemic diseases.

2. *P. gingivalis* and systemic diseases

Chronic periodontitis, a multifactorial chronic inflammatory disease resulting from dysbacteriosis, is characterized by the destruction of connective tissue and alveolar bone, and it has become the primary reason for tooth loss in adults. It affects nearly 50% of the population worldwide, representing one of the most common inflammatory diseases in humans[17]. Over the past two decades, mounting evidence has supported periodontitis as a potential risk factor for multiple systemic diseases, for example, cardiovascular diseases. As the key etiological agent in periodontitis, *Porphyromonas gingivalis* (*P. gingivalis*) has proved to be closely correlated with the occurrence and development of many systemic diseases, such as atherosclerosis, cancer, and Alzheimer's disease[18][19][20]. The roles of *P. gingivalis* in systemic diseases have been discussed for several years. In this review, we systematically and comprehensively provide an update and summary of the literature on *P. gingivalis*-related systemic diseases that affect the whole body, as well as the internal mechanisms, to provide a more comprehensive understanding of *P. gingivalis* and its relationship with systemic diseases.

2.1 Atherosclerotic cardiovascular diseases (ACVDs)

ACVDs, including coronary artery disease and stroke, are a form of CVDs with high morbidity and mortality rates. Atherosclerosis (AS), resulting from the progressive accumulation of lipids, calcium, macrophages, and other components in the artery wall, is the pathological basis of ACVDs. Trials in humans have found P. gingivalis in clinical samples at a detection rate of 82.61% by fluorescent in situ hybridization assay[21]. Subsequently, in vivo experiments confirmed the promoting effect of P. gingivalis on AS. Infection with P. gingivalis exacerbated atherogenesis in apolipoprotein E (ApoE)-deficient mice[18][21], and the proximal aortic lesion size in P. gingivalis-inoculated mice was 2-fold larger than that in control mice[18].

Most scholars regard AS as an excessive inflammatory response after arterial wall endothelial dysfunction resulting from many damage factors. The pathogenesis mechanisms of AS are highly complex and include the activation of endothelial cells and platelets, recruitment of leukocytes (mainly monocytes and macrophages), migration and proliferation of smooth muscle cells (SMCs), and formation of a lipid core, along with thrombosis and plaque instability. Studies have shown that *P. gingivalis* can promote AS by affecting the function of all of these cells . First, *P. gingivalis* can activate endothelial cells and induce endothelial dysfunction. As reported in a previous review, *P. gingivalis* invades endothelial cells via the autophagic pathway while suppressing apoptosis [22]. Through the NF-κB or p38 MAPK pathway, its fimbria and LPS positively upregulate the expression of various adhesion molecules in endothelial cells, such as vascular cell adhesion molecule-1, intercellular adhesion molecule-1, monocyte chemoattractant protein, P-selectin, and E-selectin[23] [24]. This is an essential step in the pathogenesis of endothelial dysfunction. In recently published research, it was revealed that *P. gingivalis* enhanced oxidative stress and the inflammatory response in aortic endothelial cells via the NF-κB-BMAL1-NF-κB signaling loop, leading to the aggravation of AS[21] . Furthermore, *P. gingivalis* can induce procoagulant effects in endothelial cells, and this prothrombotic response may be associated with plaque progression and instability[25]. Second, it has been reported that IgG-opsonized *P. gingivalis* may bind to the FcγRIIa receptor on platelets and activate GPIIbⅠIIa integrin, which becomes connected to Hgp44 adhesin through a fibrinogen bridge, inducing further platelet activation and aggregation[26]. A recent review analyzed the interactions of *P. gingivalis* with activated platelets, and the overall outcome may be the modified expression of CKs, which might affect the inflammatory response and fibrinolysis[27]. Third, *P. gingivalis* and its virulence components (such as LPS, fimbria) are involved in each phase of monocyte activity during the formation of AS by supporting monocyte migration to the endothelial surface, intimal infiltration, and differentiation into pro-inflammatory macrophages and eventually foam cells[28][29]. Fourth, *P. gingivalis* can play a distinct role in foam cell formation, which is a critical step in the atherosclerotic process. *P. gingivalis* LPS promotes the accumulation of lipids in macrophages and the formation of macrophage-derived foam cells by upregulating CD36 (a scavenger receptor for low-density lipoprotein and oxidized low-density lipoprotein) as a result of c-Jun/AP-1 pathway activation and by downregulating ATP-binding cassette transporter A1 (cholesterol efflux moderator) due to increased calpain activity[29]. A study in 2019 experimentally determined that *P. gingivalis* promoted lipid uptake in macrophages by inducing the expression of fatty acid-binding protein 4, which may be dependent on the JNK pathway[30]. In addition, *P. gingivalis* enhanced the TLR2-CD36/SR-B2-dependent systemic release of IL-1β, leading to a subsequent increase in lipid uptake by macrophages and foam cell formation as a result of encountering IL-1β in the vessel wall[31]. Furthermore, the proteolytic activity of Rgp and Kgp was shown to induce lipid peroxidation and to change the expression of low-density lipoprotein and high-density lipoprotein, causing foam cell formation from macrophages[32]. Evidence from these studies suggests that lipoproteins play a key role in the connection between *P. gingivalis* and AS progression. *P. gingivalis* infection may also contribute to AS by modulating lipid metabolism and homeostasis. Fifth, vascular calcification is a prominent feature of AS. *P. gingivalis* LPS can stimulate the proliferation and calcification of SMCs, resulting in vascular calcification[33]. *P. gingivalis* OMVs were also reported to promote vascular SMC calcification through ERK1/2-RUNX2[34]. Additionally, WADA et al. proposed a putative molecular mechanism in which *P. gingivalis* could contact or

invade the SMC layer in blood vessels after endothelial cell injury and induce the expression of S100A9 (a member of the S100 calcium-binding protein family), which triggers the transformation of SMCs from a contractile to a proliferative phenotype, stimulating further cell growth and contributing to aortic intimal hyperplasia[35].

2.2 Oral squamous cell carcinoma (OSCC)

OSCC often occurs in the tongue, floor of the mouth, buccal mucosa, and gingiva. A meta-analysis revealed that periodontitis increased the risk of OSCC by nearly 2-fold[36]. Furthermore, *P. gingivalis* was shown to increase the chance of OSCC, and its colonization in tumor tissues has reduced patient survival[37]. The detection of *P. gingivalis* by immunohistochemical staining was more than 33% higher in gingival carcinoma tissues than in normal gingival tissues[38]. Afterwards, in vivo experiments further confirmed the negative effect of *P. gingivalis* in OSCC. It was found that *P. gingivalis* accelerated OSCC progression in an immune microenvironment through the secretion of CCL2, CXCL2, IL-6, and IL-8 from infected oral dysplastic keratinocytes to recruit myeloid-derived suppressor cells[37]. In addition, oral administration of *P. gingivalis* promoted 4-nitroquinoline-1-oxide-induced tongue tumorigenesis and aggravated the disturbance of fatty acid metabolism during oral carcinoma progression[19].

Large studies have explored the mechanisms of *P. gingivalis* in OSCC, including epithelial–mesenchymal transition (EMT) of oral epithelial cells, the inhibition of epithelial cell apoptosis, the promotion of immune evasion, the proliferation and invasion of tumor cells, and so on . First, *P. gingivalis* upregulates the levels of zinc-finger E-box-binding homeobox proteins (ZEB1 and ZEB2), which are transcription factors that regulate EMT through GSK-3β[39] and β-catenin/forkhead box-O1 (FOXO1), respectively[40]. A review by Olsen provided a summary of evidence related to P. gingivalis-induced EMT of OSCC cells and human primary oral epithelial cells[41]. Second, P. gingivalis modulates epithelial cell apoptosis via multiple anti-apoptotic/survival pathways, including the activation of the PI3K/Akt and JAK/Stat pathways, release of survivin, upregulation of anti-apoptotic Bad and Bcl-2, downregulation of pro-apoptotic Bax, and inhibition of cytochrome c release and caspase-9 and caspase-3 activation[42][43]. *P. gingivalis* infection upregulates miR-203, which directly inhibits suppressor of cytokine signaling 3 and leads to increased Stat3 activation[44], which may also be involved in the anti-apoptotic mechanism of the epithelium, given the role of Jak/Stat mentioned above. In addition, nucleoside diphosphate kinase (NDK), an ecto-ATPase secreted by intracellular *P. gingivalis*, confers epithelial cells with an anti-apoptotic phenotype by binding to and phosphorylating HSP27, which inhibits cytochrome c release and caspase-9 activation[45]. NDK from *P. gingivalis* can also scavenge ATP and inhibit P2X7-mediated host-cell apoptosis[46]. Moreover, *P. gingivalis* infection promotes a prosurvival phenotype in human primary oral epithelial cells by regulating cyclins and p53[47]. *P. gingivalis*-induced ROS activates the multipurpose transcriptional regulator FOXO1 via JNK signaling and then initiates an anti-apoptotic program in epithelial cells[48]. Third, internalized *P. gingivalis* upregulates the expression of B7-H1 and B7-DC receptors on oral cancer cells via a receptor-interacting serine/threonine-protein kinase 2-dependent mechanism, contributing to the escape of tumor cells from immunosurveillance[49]. Furthermore, NDK from *P. gingivalis* has antagonist effects on ATP activation of P2X7 receptors, leading to reduced IL-1β production in epithelial cells, thereby promoting the immune evasion of tumor cells[50]. Fourth, *P. gingivalis* promotes the proliferation of OSCC cells by regulating the expression of cyclin D1 through the miR-21/PDCD4/AP-1 negative signaling pathway[51]. Fifth, *P. gingivalis*-infected OSCC cells can increase invasiveness through EMT-like changes[52]. In addition to EMT, *P. gingivalis* may have the ability to induce proMMP9 expression via ERK1/2-Ets1, p38/HSP27, and PAR2/NF-kB pathways, which subsequently activate MMP9, promoting OSCC cell invasion[53]. *P. gingivalis* exposure also increases the invasive ability of oral cancer cells via the upregulation of MMPs in an IL-8-dependent fashion, including MMP-1, MMP-2, and MMP-10[52][54]. Beyond the mechanisms mentioned above, it has been reported that inflammatory mediators elicited by P. gingivalis could induce cell proliferation, mutagenesis, oncogene activation, angiogenesis, and immunosuppression, thus facilitating the development of OSCC[55].

2.3 Alzheimer's Disease (AD)

AD is a neurodegenerative disease. It is the most common reason for dementia and is becoming a major health problem in aging societies worldwide. A historical cohort study found that chronic periodontitis patients had an elevated risk of AD[56], and *P. gingivalis* DNA, LPS[57], and gingipains[58] have been identified in AD brains. Parallel epidemiological studies and animal experiments also strengthen support for the possible relevance of *P. gingivalis* in AD pathogenesis. *P. gingivalis* exposure induced AD-like phenotypes in mice, which presented as microglia-mediated neuroinflammation, β-amyloid (Aβ) accumulation in neurons, impaired cognitive function, and a reduction in learning and memory[59][60].

The pathology of AD has three major hallmarks: Aβ plaques, neurofibrillary tangles, and microglia-mediated neuroinflammation. *P. gingivalis* may be involved in the progression of AD through these processes. Cathepsin B (CatB) is crucial for Aβ deposition and the mediation of neuroinflammation. Intraperitoneal injection of *P. gingivalis* LPS into middle-aged WT mice significantly increased CatB expression in both microglia and neurons, and *P. gingivalis* LPS-induced AD-

like phenotypes were found to occur only in a CatB-dependent manner[59]. Furthermore, in *P. gingivalis*-infected mice, Aβ accumulated in inflammatory monocytes/macrophages, mainly based on CatB/NF-κB signaling activation, and this is the first evidence to suggest that inflammatory monocytes/macrophages act as the source of peripheral Aβ when exposed to *P. gingivalis*[61]. Therefore, considering the pivotal role of CatB, it has been regarded as a potential therapeutic target for preventing *P. gingivalis*-associated cognitive decline in AD[59][61]. In addition, hippocampal neurons had significantly increased mean mRNA levels of amyloid precursor protein and CatB when treated with conditioned medium from *P. gingivalis* LPS-treated WT primary microglia, but not when treated with *P. gingivalis* LPS directly[59]. Accordingly, the pivotal, detrimental role of *P. gingivalis* against microglia is involved in the pathogenesis and development of AD. A recent review indicated that P. gingivalis may affect microglia and genes such as apolipoprotein, clusterin, CD33, and complement receptors to cooperatively promote the neurodegeneration that is typical of AD[62]. Furthermore, *P. gingivalis* LPS might induce neuroinflammation and cognitive impairment in mice via the TLR4/NF-κB signaling pathway[60]. In addition to the direct role of *P. gingivalis*, the release of inflammatory molecules may also be involved. Various host cells infected with *P. gingivalis* reportedly release a set of CKs, such as TNF-α, IL-1, IL-6, and IL-8, in their immune response[63]. Pro-inflammatory mediators could reach the central nervous system via hematoencephalic barrier-free areas and fenestrated capillaries or by regulating blood–brain barrier permeability[64]. Systemic inflammation, including inflammatory mediators such as CRP, TNF-a, IL-6, and IL-1β, may also increase the risk and progression of cognitive decline and AD. In contrast to the above-described studies, Liu et al. focused on gingipains, Rgp and Kgp. They revealed that gingipains cooperatively contributed to the cell migration of microglia towards the infected site and induced neuroinflammation through the proteolytic activation of PAR2, and the subsequent activation of PI3K/Akt and MEK/ERK pathways may also play fundamental roles in this process[65]. In addition, researchers have proposed that P. gingivalis may also be involved in the progress of AD by contributing to the suppression of the host's adaptive immune system. P. gingivalis could prevent the entry of immune cells into the brain, increase blood–brain barrier permeability, and inhibit the local IFN-γ response. The scarcity of adaptive immune cells in AD neuropathology further implies that P. gingivalis residing in the brain may impair clearance of Aβ and induce immunosuppression[66].

2.4 Diabetes

Diabetes, a series of chronic metabolic disorders characterized by hyperglycemia, is the result of defects in insulin secretion, insulin action, or both. Considerable epidemiologic evidence has shown a two-way interrelationship between periodontitis and diabetes, and many researchers regard periodontal infection as a risk factor for diabetes progression. Diabetic individuals with periodontitis were found to have a significantly higher prevalence of diabetes-related complications[67].Further animal experiments have confirmed that *P. gingivalis* or its components can induce insulin resistance in mice[68][69][70][71], which is one of the vital pathogeneses of type 2 diabetes.

Among the potential *P. gingivalis*-related mechanisms involved in the course of diabetes, insulin resistance is considered to be the most important. *P. gingivalis* infection increased systemic inflammation, especially in adipose tissue, through the induction of endotoxemia [69], alteration of gut microbiota[72], or an impaired regional adaptive immune response [68], ultimately resulting in insulin resistance. Moreover, inflammation and elevated levels of inflammatory markers, such as CRP and IL-6, can induce insulin resistance[73]. Thus, increased levels of systemic pro-inflammatory CKs initiated by *P. gingivalis* may promote insulin resistance. *P. gingivalis* LPS induced pro-inflammatory adipokine secretion and oxidative stress in adipocytes through the regulation of TLR-mediated pathways and redox enzymes and contributed to obesity-associated insulin resistance[74]. A recent study in 2020 indicated that *P. gingivalis* aggravated high-fat diet (HFD)-induced insulin resistance in mice via its biosynthesis of branched-chain amino acids, which can activate the mammalian target of rapamycin and downstream genes, which leads to the dephosphorylation of insulin receptor substrate 1[71]. Furthermore, *P. gingivalis* OMVs were loaded with gingipains and translocated to the liver in mice, leading to the attenuation of insulin sensitivity and inhibition of hepatic glycogen synthesis, partly by attenuating the Akt and GSK-3β pathway[70]. Importantly, potential mechanisms other than insulin resistance should be examined. Higher colonization levels of *P. gingivalis* are reported to be linked to higher prediabetes prevalence among diabetes-free adults[75]. *P. gingivalis* LPS stimulated insulin secretion by pancreatic β-cells and had significant implications in the progression of β-cell compensation in prediabetes in subjects with periodontitis[76]. Moreover, oral administration of *P. gingivalis* induced the translocation of *P. gingivalis*/gingipains to the pancreas in mice, leading to significant changes in islet architecture and β-cell apoptosis, which may be involved in the development of prediabetes[77]. Lastly, *P. gingivalis* attenuated the phosphorylation and translocation of FOXO1, which is regulated by insulin in HepG2 cells, thereby increasing hepatic gluconeogenesis[78] and potentially leading to elevated blood glucose.

3. Conclusion

The latest studies have tended to focus on exploring possible direct and indirect links between P. gingivalis and certain systemic diseases, especially AD and AS, and an increasing amount of evidence has been accumulating. *P. gingivalis* invades the human body and influences general health in four main ways (**Figure 1**). (i) Bacteremia: The direct invasion of *P. gingivalis* in epithelium, endothelial cells, and subepithelial tissues has been demonstrated[79]. Transient bacteremia of P. gingivalis frequently occurs during daily activities, such as toothbrushing, chewing, and flossing, and after dental treatment procedures[10], which enable the bacteria to enter the rest of the body and take part in local pathogenesis. (ii) Immunologic sounding: Persistent local infection caused by *P. gingivalis* induces the upregulation of inflammatory cascades involving IL-1, IL-6, IL-8, TNF-α, CRP, and IFN[63]. A low-level, long-term systemic inflammatory status might be implicated in the pathology of systemic disorders. (iii) Specific toxins of *P. gingivalis*, such as gingipains and OMVs, have been detected at multiple body sites (such as the brain and liver) and play pivotal roles in the progression of local diseases[58][70]. (iiii) Pathogen trafficking: Direct infection and internalization in host immune cells, such monocytes, and subsequent recruitment to tissues throughout the whole body may be another pathogenic strategy of *P. gingivalis*[58].

Figure 1. Strategies by which *Porphyromonas gingivalis* can invade the whole body, along with simple a schematic representation of *Porphyromonas gingivalis*-associated systemic diseases.

In this article, we comprehensively summarize the adverse effects of *P. gingivalis* on multiple systems and a variety of diseases. Some of the clearer and more direct mechanisms are discussed here. However, many of the exact mechanisms are not fully clear yet, and a few conclusions are controversial. Current evidence emphasizes that promoting oral health should be encouraged as an indispensable part of a healthy lifestyle to reduce the burden of global chronic noncommunicable and communicable diseases[80], which was an initiative of the World Health Assembly as early as 2007. There is currently no doubt that periodontitis is certainly preventable and controllable, as is *P. gingivalis*, and should be regarded as a modifiable factor for diseases. Reducing the load of *P. gingivalis* through periodontal intervention has potential benefits for oral health and a direct or indirect positive impact on overall health, even if it prevents the possibility of such a connection. We should be aware of the risk and address it as soon as possible to avoid threatening our health. Moreover, interrelations between *P. gingivalis* and other oral pathogens (such as *Actinobacillus actinomycetemcomitans* and *Fusobacterium nucleatum)*, together with gut microbiota, are another subject of intensive study.

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