



## *Porphyromonas gingivalis* and its impact on periodontal health and systemic diseases. A concise review.

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### ABSTRACT

Periodontitis is defined as a multifactorial chronic inflammatory disease, associated to a dysbiotic biofilm and characterized by the progressive destruction of the periodontal attachment. Clinical studies have revealed the presence of 10 to 15 bacterial species that are potential periodontal pathogens in adults. From these, the most cited are *Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans* and *Tannerella forsythia*. The aim of this article is to review *P. gingivalis*' characteristics and impact on periodontal and systemic health. Different studies have reported a relation between the presence of *P. gingivalis* and periodontal disease. *P. gingivalis* was one of the most frequently detected species in aggressive and chronic periodontitis. This is due to its unique ability to avoid the host's immune response and contribute to the development of the destructive process. *P. gingivalis*, although only present in low frequency, is pathogenic because of its ability to induce dysbiotic microbial communities. There is more evidence that *P. gingivalis* might invade cardiovascular cells and tissues causing inflammation. It has been suggested that NLRP3 inflammasome plays a key role in the development of vascular inflammation and atherosclerosis. The repeated exposure to *P. gingivalis*, produces neuroinflammation, neurodegeneration and formation of intra and extracellular amyloid plaques, which are pathognomonic signs of Alzheimer's disease.

**Keywords:** *Porphyromonas gingivalis*, periodontitis, immunomodulation, systemic disease.

### INTRODUCTION

Periodontitis is defined as a multifactorial chronic inflammatory disease, associated to a dysbiotic biofilm and characterized by the progressive destruction of the periodontal attachment (Papapanou et al., 2018). The disease's physiopathology responds to the activation of key molecular pathways that lead to the activation of host-derived proteinases and the loss of fibers of the periodontal ligament (Tonetti et al., 2018). The model of polymicrobial synergy and dysbiosis suggests that the host's immune response is initially subverted by keystone pathogens aided by accessory pathogens. Then, pathobionts over-activate it and initiate destructive inflammation in susceptible individuals (Hajishengallis, 2015).

Clinical studies have revealed the presence of 10 to 15 bacterial species that are potential periodontal pathogens in adults. From these, the most cited are *Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans* and *Tannerella forsythia*. There are few data regarding the prevalence of these pathogens in the plaque of healthy children. The presence of these three main periodontal pathogens, in health and sickness, suggests that other factors might be responsible for causing the disease. This proves the principles of the ecological plaque hypothesis, which proposes that organisms related to the disease might be present in healthy zones (Gafan et al., 2004).

The aim of this article is to review *P. gingivalis*' characteristics and impact on periodontal and systemic health.

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**Receipt:** 07/04/2019

**Revised:** 07/09/2019

**Acceptance:** 08/28/2019

**Online:** 08/28/2019

**Conflict of interests:** None.

**Ethics approval:** Not required.

**Funding:** None.

**Authors' contributions:** All authors carried out the entire review.

**Acknowledgements:** None.

**doi:** 10.32457/ijmss.2019.010.

## PORPHYROMONAS GINGIVALIS

*P. gingivalis* is a Gram-negative black pigmented anaerobic bacterium that resides in the subgingival crevice and is considered a key etiological factor in periodontal diseases along with other oral pathogens (Sanchez et al., 2015). It is considered as such because it produces a series of virulence factors and extracellular proteases such as lipopolysaccharides, fimbriae, gingipains and others, that result in the destruction of periodontal tissues (Yan et al., 2016).

Different studies have reported a relation between the presence of *P. gingivalis* and periodontal disease. *P. gingivalis* was one of the most frequently detected species in aggressive and chronic periodontitis (Feng et al., 2015). This is due to its unique ability to avoid the host's immune response and contribute to the development of the destructive process (Rafiei et al., 2017). *P. gingivalis*, although only present in low frequency, is pathogenic because of its ability to induce dysbiotic microbial communities (Takahashi et al., 2018).

*P. gingivalis'* ability to manipulate the host's immune response is crucial for inciting quantitative and qualitative alterations on the oral microbiota. This can unleash an inflammatory process with subsequent loss of periodontal bone. By degrading and inactivating antimicrobial peptides, *P. gingivalis* might provide in vivo protection to pathobionts that over-activate immune response (Hajishengallis, 2015).

## EPIDEMIOLOGY

*P. gingivalis* is in 85.75% of the samples of subgingival plaque from patients with chronic periodontitis (Yan et al., 2016). Whereas in Chile, Arce et al. (2017) detected a high prevalence of *P. gingivalis* (75.7%) in microbiological cultures, with an average 24.1% CFUs per patient. Rojas et al. (2017) found a prevalence of 73.3% in adult patients with diagnosed periodontal disease.

Ingalagi et al. (2018) found a high prevalence in healthy adult patients, as well as patients with periodontal disease. The prevalence of *P. gingivalis* was high in the group of healthy patients with 179 subjects (89.5%) compared to 109 subjects (54.0%) in the group of patients with periodontal disease. When comparing by sex, women showed a slightly higher prevalence (74%) than men (69.4%).

The prevalence of periodontal disease in children and adolescents is relatively low, approximately between 0.2% and 0.5%. Nevertheless, the different degrees of gingivitis are extremely common (Song, 2013). *Streptococcus mutans* provides a classic example that illustrates the colonization window for bacteria. Early colonization by *S. mutans* occurs in approxima-

tely 80% of the infants. However, it is still uncertain if there are groups related with age for early colonization by periodontal pathogens. Furthermore, there are no reports regarding which specific tissues of the zone, if any, might be associated with such early colonization (Cortelli et al., 2008).

*P. gingivalis* has been isolated from the plaque of 80% of children during and after puberty, while other studies weren't able to detect *P. gingivalis* in prepubertal children. *P. gingivalis* and *A. actinomycetemcomitans* have been identified in small children's plaque by using CRP test. *P. gingivalis* was detected in 40% to 50% of children between the ages of 0 and 2, but they did not show more prevalence (60%) than adolescents between the ages of 13 and 14 (Gafan et al., 2004). Takahashi et al. (2018) determined that such pathogens seem more stable in older children and values tend to be higher in children aged 6 to 9 and 12 to 18 years.

Although periodontal disease is rare in healthy children, it is important to investigate the presence of periodontal pathogens. The detection of periodontal pathogens before puberty might be useful for identifying children that need more effective oral health programs in order to minimize the risk of periodontal disease after puberty (Gafan et al., 2004).

## COLONIZATION OF P. GINGIVALIS IN CHILDREN

It has been reported that children colonized by periodontal pathogen bacteria frequently show signs of periodontal disease and that there is a correlation between colonization and periodontal disease in the mothers (Takahashi et al., 2018).

As part of the normal flora of the oral cavity, there is a great variety of microorganisms with different potential virulence factors. In these groups some Gram-negative and anaerobic species can be found, which play a key role in the etiology of periodontal disease. These include *Porphyromonas gingivalis*, *Prevotella intermedia*, *Prevotella nigrescens*, *Actinobacillus actinomycetemcomitans*, *Fusobacterium nucleatum*, *Eikenella corrodens* and *Treponema denticola*. The colonization of periodontopathogens in the oral cavity during childhood remains an unanswered question in the literature. It has been suggested that periodontal pathogens might be transmitted by parents, especially the mothers during childhood. Early colonization in children is a reflection of the parents' eating and hygiene habits, which relates to the concept of window of infectivity. This corresponds to a period in which the host is exposed to a transmission vehicle contaminated with a given microbial species and, thus, colonized more easily, which might explain the future relation between such pathogen and the host (Takahashi et al., 2018).

However, Rotimi et al. (2010) stated that, unlike most oral anaerobes, true periodontal pathogens generally cannot colonize

the oral cavity in early childhood but later in life. Presence of *P. gingivalis* in children's saliva has been confirmed, although in considerably low proportions. Therefore, they suggest that the prevalence of *P. gingivalis*, *P. intermedia* and *T. forsythia* might be temporal and their colonization in children without periodontal disease may be a rare event. It must be noticed that the continuous presence of these pathogens is probably a prerequisite for periodontal disease. Finally, these researchers suggest differentiating the prevalence between saliva and gingival crevicular fluid samples for a more concrete assessment in terms of periodontal risk.

## **P. GINGIVALIS AND IMMUNE MODULATION**

*P. gingivalis* has proven to have different modulation mechanisms of innate immunity by limiting the activation of NLRP3 inflammasome. One of them, ATP- / P2X7 receptor signaling, has been recently linked not only to periodontitis but also to the development of different systemic diseases. According to this, the importance of inflammasomes is that they are responsible for the maturation of pro-inflammatory cytokines, such as interleukin-1 $\beta$  (*IL-1b*) and IL-18, as well as the activation of inflammatory cell death, called pyroptosis (Olsen & Yilmaz, 2016).

Gingival epithelial cells, from which inflammasomes derive, are an important part of the immune response to periodontal bacteria. They express a functional inflammasome, NLRP3. Much higher levels of inflammasome components were found in gingival tissue of patients with chronic periodontitis than in healthy controls. Therefore, it seems reasonable to consider inflammasome as an operating part of innate immunity against periodontitis and its relation to systemic diseases (Olsen & Yilmaz, 2016).

Inflammasomes are assembled in response to cell infection, cell stress or tissue damage, they promote inflammatory responses and are quite significant for the regulation of the innate immune system in chronic inflammatory diseases, such as periodontitis and different systemic diseases. In this regard, it has been proven that many opportunistic pathogens develop different mechanisms for inhibiting the activation and function of inflammasome. Likewise, it has been found that *P. gingivalis* manipulates innate immunity through different mechanisms (Olsen & Yilmaz, 2016).

*P. gingivalis* can also suppress inflammasome activation for *F. nucleatum* and this can be a contribution from *P. gingivalis* to the synergy between the two periodontal diseases. This specific inhibition seems to affect the processing of IL-1 $\beta$  and IL-18 and cell death in macrophages from humans and mice. Whereas *F. nucleatum* activated the processing of IL-1 $\beta$  through NLRP3 inflammasome, the repression mediated by *P. gingivalis* was not correlated with the low levels of inflammasome components (Ol-

sen & Yilmaz, 2016).

Infection by *P. gingivalis* also has an impact on endocytosis, by preferably suppressing endocytic pathways towards the activation of the inflammasome. This represents a new pathogen-mediated inhibition mechanism of inflammasome (Olsen & Yilmaz, 2016). *P. gingivalis*, once established in the nutrient rich cytosol of the host cell, can protect the infected cell from the host's immune defense by reducing inflammatory response. This occurs through the temporary externalization of phosphatidylserine, which when exposed to the medium is considered an early apoptosis marker associated with the pro-inflammatory activation of the complement (Yilmaz et al., 2004). This would allow the multiplication of *P. gingivalis* within the cells, while it protects them from the cytotoxic reaction of the immune system. It has also been suggested that the bacterium blocks mitochondrion-dependent apoptosis in order to maintain its intracellular lifestyle. This might allow the successful propagation of *P. gingivalis* to the adjacent and deeper tissues of the host.

*P. gingivalis* uses its homologous from extracellularly secreted nucleoside-diphosphate kinase for inhibiting innate immune responses due to stimulation by extracellular ATP (*eATP*). Extracellular ATP acts as a danger signal that can alert the immune system in case an infection appears. Extracellular ATP joins P2X7 receptors by activating an inflammasome and caspase 1. The infection of gingival epithelial cells resulted in ATP inhibition induced by caspase-1 activation so that the danger signal is completely inhibited by the bacterium (Olsen & Yilmaz, 2016).

Recently, it has been proven that *P. gingivalis* can also use danger signal adenosine via adenosine A2A receptor as a means to proliferate and survive in primary gingival epithelial cells, possibly through the negative regulation of the pro-inflammatory response (Olsen & Yilmaz, 2016).

## **P. GINGIVALIS AND SYSTEMIC DISEASES**

There is more evidence that *P. gingivalis* might invade cardiovascular cells and tissues causing inflammation. It has been suggested that NLRP3 inflammasome plays a key role in the development of vascular inflammation and atherosclerosis. Tests on hyperlipidemic animals have shown that *P. gingivalis* accelerates the atherosclerosis process. On the other hand, fimbriae were found to increase tissue invasiveness and *P. gingivalis'* pro-inflammatory ability (Olsen & Yilmaz, 2016).

In vascular cells and atherosclerotic lesions, AIM2 might play a role in vascular pathogenesis. A greater expression of AIM2 around the necrotic nucleus of carotid atherosclerotic lesions and in the *vasa vasorum* of aortic aneurysms neovascularization. Therefore, NLRP3 inflammasome and AIM2 might play key roles in *P. gingivalis*-induced periodontal disease as well as in atheros-

clerosis through sustained inflammation (Olsen & Yilmaz, 2016).

Alzheimer's disease (AD) is the most common form of dementia. It is clinically characterized by a progressive decrease in the cognitive function, which starts with memory deterioration and can continue to organic dysfunction in the patient. Recently, a possible relation between periodontal disease and AD has been reported. Oral infections by *P. gingivalis* or the introduction of a lipopolysaccharide (LPS) into the blood stream might affect the neural system (Singh et al., 2015). Presence of NLRP3 in microglial cells that responded to the infection and at the beginning of neurodegeneration in an AD model has been reported. Additionally, it has been recently discovered that TLR2 and NLRP3 cooperate in order to recognize a functional bacterial amyloid, curli fibers, in brain plaques from AD patients. Strongly active expression of caspase-1 was found in human mild cognitive impairment and brains with AD, which suggests a role of inflammasome in brain degenerative disease. AD's brain deposits activated NLRP3 inflammasome in in vitro and in vivo microglial cells, which might lead to the progression of AD (Olsen & Yilmaz, 2016).

In young adult wild type mice, the repeated exposure to *P. gingivalis*, administered orally, produces neuroinflammation, neurodegeneration and formation of intra and extracellular amyloid plaques, which are pathognomonic signs of AD. The neuropathological features observed strongly suggest that low degree chronic inflammation by periodontal pathogens might result in the development of a neuropathology that is consistent with the one from AD (Ilievski et al., 2018).

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