Research progress on the correlation between porphyromonas gingivalis and human diseases

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Abstract: *Porphyromonas gingivalis is a Gram-negative anaerobic bacterium that is closely related to periodontal diseases and has strong virulence. Studies have shown that in addition to damaging oral health, it also has a serious impact on general health. This article reviews the research progress of the relationship between Porphyromonas gingivalis and human diseases, which is helpful to explore new treatment strategies for related diseases.*

Keywords: *Porphyromonas gingivalis, Periodontitis, Neoplasms, Dental plaque biofilms*

Human microbial colonization is mainly distributed in four parts (intestinal tract, oral cavity, skin and vagina) [1]. Oral microbiota is the second most diverse microbiome in human body after gut [2]. At present, more than 700 microorganisms have been identified in the oral cavity, including bacteria, fungi, viruses, chlamydia and mycoplasma [3]. Porphyromonas gingivalis (P. gingivalis) is one of the main pathogens causing the development of periodontitis. It adheres to periodontal tissues with pili and participates in the formation of plaque biofilm with other bacteria. It can damage periodontal tissue, form the signature periodontal pocket, and even lead to tooth loosening and loss [4]. Porphyromonas gingivalis can affect and invade the body through a variety of ways. Therefore, Porphyromonas gingivalis is associated with the pathogenesis of multiple organ and systemic diseases. This article discusses the role of P. gingivalis in the pathogenesis of systemic diseases, and reviews the research progress of the relationship between P. gingivalis and human systemic diseases in recent years.

1. Porphyromonas gingivalis and oral diseases

With the continuous development of detection technology, we have begun to explore the oral microbiome and discover its complexity, gaining new insights into its role in health and disease. In general, the microorganisms in the oral cavity maintain a balance with the human body. When the balance is broken by various factors, the proliferation of disease-causing bacteria is promoted, leading to the occurrence of periodontitis, dental caries and even tumors [5].

Periodontitis is a chronic inflammatory disease of the oral cavity, which is mainly manifested by the destruction of periodontal supporting tissues and is the main cause of tooth loss in adults [6]. Dental plaque biofilm was used as the initiating factor. Five main complexes were observed in the subgingival plaque, especially the red complex (including Porphyromonas gingivalis and Tannerella forsythia, Treponema denticola) [7]. Porphyromonas gingivalis is one of the main pathogens of periodontitis, which can lead to periodontal microecological imbalance and alveolar bone resorption. It possesses a variety of virulence factors, such as fimbriae, gingivalis, lipopolysaccharide, and outer membrane vesicles. It can quickly adhere to and invade a variety of host cells and cause damage to host tissues. It can also activate certain signaling pathways or regulate the expression of signaling molecules, thus triggering the immune inflammatory response of the host, causing periodontal tissue damage and even systemic diseases [8].

Dental caries is a common oral disease with an incidence of about 7.5%. There is no statistically significant difference in the proportion of males and females. There is a certain relationship with age, most of them are children, and children's diet and living habits are more likely to lead to the occurrence of dental caries. The positive rate of P. gingivalis infection in patients with dental caries is higher than that in healthy people, suggesting that P. gingivalis infection is one of the key risk factors leading to dental caries [9]. This may be related to the fact that P. gingivalis has lipopolysaccharide, outer membrane protein and other structures, which escape from the host immune defense function. After P.

gingivalis infection in the oral cavity, it causes oral inflammatory response, chronic destruction of teeth, formation of cavities, and destruction of the crown until the crown disappears. At the same time, the toxin produced by P. gingivalis causes the oral mucosa to produce related inflammatory response, which accelerates the development of dental caries [10].

Oral squamous cell carcinoma (OSCC) is the sixth most common malignant tumor. It is characterized by high incidence, low survival rate, poor prognosis, and easy recurrence. Chronic inflammation plays an important role in all stages of tumor development and is mainly caused by infection or environmental factors. P.gingivalis causes chronic inflammation through a variety of pathways. After P.gingivalis infects oral epithelial cells, it stimulates inflammatory cells to produce reactive oxygen species, reactive nitrogen intermediates, inflammatory cytokines, etc. These products can promote mutations by damaging DNA, reducing gene stability, and changing genetics, and then promote cell carcinogenesis [11]. Studies [12] have shown that P. gingivalis infection of Gingival epithelial cells (GECs) can lead to a decrease in p53 level. p53 can arrest the cell cycle and repair DNA, and can also cause apoptosis, and is a tumor suppressor. It plays an important role in the cellular response to DNA damage and other genomic aberrations. The PI3K pathway is another important component in the regulation of cell cycle progression. P. gingivalis infection increased the levels of PI3K and phosphatidylinositol-dependent protein-serine kinase 1 (PDK1), which coupled PI3K to cell proliferation and survival signaling through activation of Akt, PKC isoenzymes, p70S6K, and p90RSK. These results suggest that P. gingivalis activates the PI3K/Akt pathway in GEC and is associated with anti-apoptotic cell death. Increased GEC proliferation caused by P. gingivalis infection may have significant effects on gingival integrity and repair in vivo. In order to evaluate the role of bacteria in the development of oral squamous cell carcinoma (OSCC), Pushalkar et al. [13] cultured and identified bacteria from saliva samples of OSCC subjects. These bacteria may cause inflammation and support the progression of OSCC. Bacterial profiles of OSCC and controls were determined by 16S rDNA gene detection. The results showed that a variety of bacteria including P. gingivalis were more common in the OSCC group. In 2011, some scholars [14] used immunohistochemical staining to observe the expression of P. gingivalis and Streptococcus in gingival specimens of patients with oral squamous cell carcinoma. In the samples of OSCC gingiva (n=10) and normal gingiva (n=5), P. gingivalis was detected in both normal and cancer tissues, with higher levels in cancer samples (more than 33%, P<0.05), and the staining intensity of P. gingivalis was twice that of Streptococcus SPP. P. gingivalis is abundant in malignant oral epithelium, suggesting a potential association between P. gingivalis and oral squamous cell carcinoma.

2. Porphyromonas gingivalis and respiratory diseases

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable respiratory disease characterized by airflow obstruction. Yu et al. [15] conducted a study on the distribution of rag genotypes of Porphyromonas gingivalis in patients with chronic periodontitis and chronic obstructive pulmonary disease (COPD). The detection rates of Rag-1 genotypes in the two groups were 70% and 30.77%, respectively, and the difference was statistically significant (P<0.05). There was no significant difference in the detection rate of rag-2, rag-3 and rag-4 between the two groups. It is suggested that Rag-1 may be more closely related to the development of COPD. P. gingivalis exerts virulence through susceptible hosts and is influenced by factors such as genotype.

Porphyromonas gingivalis is associated with lung cancer. Liu et al. [16] found that the detection rate of Porphyromonas gingivalis in lung cancer tissues was significantly higher than that in adjacent lung tissues, suggesting that the microenvironment of cancer cells is more conducive to the survival of P. gingivalis. P. gingivalis infection is closely related to smoking, drinking, lymph node metastasis and clinical stage. The survival rate and median survival time of lung cancer patients with P. gingivalis infection were significantly shortened. Long-term smoking and drinking may increase the risk of P. gingivalis infection, and P. gingivalis infection may promote the progression of lung cancer.

3. Porphyromonas gingivalis and digestive tract diseases

Increasing evidence suggests a causal relationship between specific bacterial infections and the development of certain malignancies. P. gingivalis infection may be a high risk factor for esophageal squamous cell carcinoma [17]. Some scholars [18] evaluated 156 cases of esophageal squamous cell carcinoma (ESCC) by immunohistochemical method, and found the presence of P.g in about 57% of the patients' esophageal tissues. The microbiota profile showed that the abundance of P. gingivalis was

associated with an increased risk of ESCC development, and the presence of P. gingivalis was associated with advanced clinical stage and poor prognosis. Studies have shown that P. gingivalis may promote the occurrence and development of esophageal cancer.One study[19] used immunohistochemical method to detect the infection status of P. gingivalis and the expression of Beclin1 in 370 patients with esophageal squamous cell carcinoma. The results showed that P. gingivalis infection was negatively correlated with the expression of Beclin1 in ESCC tissues. P. gingivalis infection and low expression of Beclin1 were significantly correlated with the differentiation, depth of tumor invasion, lymph node metastasis, clinical stage and prognosis of ESCC patients. P. gingivalis infection and Beclin1 knockdown enhanced the proliferation, migration and anti-apoptosis of ESCC cells (KYSE150 and KYSE30). These results suggest that P. gingivalis infection and low Beclin1 expression are associated with the development and progression of ESCC.

In 2003, the first national health and nutritionexamination surveysI (NHANESI) epidemiological follow-up study in the United States included the study on the relationship between periodontal disease and pancreatic cancer [20]. NHANES III also showed an association between P. gingivalis and pancreatic cancer. The NHANES III epidemiological study showed that serum P. gingivalis IgG antibody was associated with gastrointestinal tumors. P. gingivalis is associated with gastrointestinal tumors and is independent of periodontal disease. P. gingivalis is expected to be a microbial marker for digestive tract tumors.P. gingivalis has been found to invade the host immune system through cytokine and receptor degradation and disrupt signaling pathways. P. gingivalis and Actinomycetes can both activate Toll-like receptor (TLR) signaling. TLR is an important promoter in animal models of pancreatic cancer [21]. Oral microbiota, periodontal disease and tooth loss play important roles in the occurrence of pancreatic cancer. A 2014 prospective cohort study [22] examined the association between antibodies to 25 oral bacteria and the risk of pancreatic cancer. Oral bacterial antibodies were measured in prediagnostic blood samples from 405 patients with pancreatic cancer and 416 matched controls. Individuals with high levels of antibodies against P. gingivalis ATTC 53978, a pathogenic periodontal bacterium, were found to have a 2-fold higher risk of developing pancreatic cancer than individuals with lower levels of these antibodies. Periodontal disease may increase the risk of pancreatic cancer. In addition, increasing the level of antibodies against specific commensal oral bacteria, which can inhibit the growth of pathogenic bacteria, may reduce the risk of pancreatic cancer. How P. gingivalis, as an important pathogen of periodontitis, affects the progression of pancreatic cancer needs to be further studied.

4. Porphyromonas gingivalis and immune system diseases

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic inflammation and damage to joint tissues. Previous studies have demonstrated an increased incidence of periodontitis in patients with rheumatoid arthritis (RA), and treatment of periodontitis can reduce RA activity. It has been proposed that periodontal disease and rheumatoid arthritis are linked by periodontal pathogens. In a 2018 study [23], significant differences in subgingival bacterial communities were found between RA patients and controls. Patients with RA have higher bacterial loads, higher abundance of pathogenic species, and more diverse microbiota. The homeostasis of microbiota can be regulated by a series of parameters such as genetics, environment and inflammatory factors. The chronic systemic inflammation in RA may affect the inflammation level of periodontal tissue, and then change the periodontal bacterial community. The levels of IL-2, IFN-γ, TNF and IL-33 were approximately 2-fold higher in RA patients without periodontitis than in controls. IL-33 stimulates Th2 responses, whereas IFN-γ and IL-2 regulate multiple aspects of the immune response. The results showed that periodontitis and RA were interdependent, with elevated levels of proinflammatory molecules in both. Inflammatory mediators in the subgingival microenvironment may alter ecological conditions to favor the growth of pathogenic bacteria, including P. gingivalis, leading to periodontal destruction.It is not known whether oral dysbiosis precedes the onset of clinical arthritis. Anti-cyclic citrullinated antibody (CCP+) is of great significance in the diagnosis of rheumatoid arthritis. In 2020, Cheng et al. [24] selected 48 CCP+ high-risk patients, 26 early RA patients and 32 asymptomatic healthy control (HC) patients with periodontal subgingival plaque in healthy and diseased periodontal sites. The results showed that the microbial richness of the CCP+ high-risk group was significantly lower than that of the HC group and the early RA group in the periodontal healthy sites. Certain core species, including P. gingivalis, had higher relative abundance in the CCP+ high-risk group. The subgingival microbial community of anti-CCP positive high-risk group was abnormal, and the abundance of P. gingivalis was increased. Oral microbiota, especially P. gingivalis, plays an important role in the pathogenesis of rheumatoid arthritis.

A study on the effect of systemic lupus erythematosus (SLE) on subgingival flora [25] showed that SLE patients had a higher prevalence of periodontitis and a younger age of onset. More severe forms of periodontitis with higher bacterial load and decreased microbial diversity were found in SLE subjects. Bacteria associated with periodontal diseases including P. gingivalis were more prevalent in SLE patients, even in periodontal healthy sites. SLE patients with periodontitis had higher concentrations of IL-6, IL-17, and IL-33, indicating that changes in oral microbiota are associated with increased local inflammation.

5. Porphyromonas gingivalis and circulatory system diseases

Previous studies have shown an association between chronic periodontitis and the incidence of cardiovascular disease, but the specific mechanism remains unclear. Oral pathogens including P. gingivalis can cause systemic disease by entering the bloodstream or triggering immune effects locally. With the emergence of the immune-inflammatory axis, oral microecological imbalance has become a new pathogenic risk factor for the development of cardiovascular diseases (cvd), such as atherosclerosis, coronary heart disease, and valvheart disease (VHD). Evidence that oral bacteria have been found in heart valves links oral microbes to the development of valvular heart disease (VHD). The altered heart after surgery (implantation of artificial heart valves or pacemakers), trauma and changes in tissue structure lead to easy attachment of bacteria to the heart valves or the inner wall of the heart [26]. Modulation of the oral microbiota plays a beneficial role in CVD management.

In a cross-sectional study in the United States in 2020 [27], a multivariate logistic regression model was used to analyze the association between chronic periodontitis and cerebral atherosclerosis and cerebrovascular diseases [acute ischemic stroke (AIS), hemorrhagic stroke (HS) and transient ischemic attack (TIA)]. The results showed that the risk of cerebral atherosclerosis in patients with chronic periodontitis was 2.48 times higher than that in patients without chronic periodontitis, and cerebral atherosclerosis was associated with an increased risk of TIA. No significant association was found between chronic periodontitis and cerebrovascular disease. Although chronic periodontitis may not directly increase the risk of cerebrovascular disease, it increases the burden of cerebrovascular disease by clearly increasing the risk of cerebral atherosclerosis.

6. Porphyromonas gingivalis and nervous system diseases

Alzheimer's disease (AD) is the most common type of dementia, which is a neurodegenerative disease. Progressive cognitive decline and memory loss are the main manifestations, and deficits in language and visuospatial skills are accompanied by behavioral disorders such as apathy, aggression and depression [28].In a retrospective cohort study [29], Cox proportional hazards regression model was used to analyze the risk of AD, and the results showed that the prevalence of hyperlipidemia, depression, brain trauma, and comorbidities and the level of urbanization in patients with chronic periodontitis (CP) were higher than those in the non-exposed cohort (all p < 0.01). At the last follow-up, 115 cases (1.24%) in the CP-exposed group and 208 cases (1.11%) in the non-exposed group developed AD. Compared with the unexposed group, CP exposure was associated with a 1.707-fold increased risk of AD. This finding highlights the need to prevent and treat periodontitis. P. gingivalis virulence factor lipopolysaccharide (LPS), which contains a proteolytic enzyme (gingipain), is associated with outer membrane vesicles (OMVs) and may impair the integrity of the blood-brain barrier in humans, facilitating the entry of bacteria and outer membrane vesicles containing lysine-gingipain (KGP) into the brain. Moreover, it affects the local inflammatory response by preventing immune cells from entering the brain, leading to insoluble amyloid clearance disorders [30].P. gingivalis DNA and antibodies were detected in the cerebrospinal fluid and serum of human Alzheimer's disease patients, which also confirmed the above views [31]. P. gingivalis infection or administration of the P. gingivalis virulence factor lipopolysaccharide (LPS) causes production of inflammatory mediators TNF-α(tumor necrosis factor-α), IL-6(interleukin-6), and IL-1β(interleukin-1β), increases production of Aβ(amyloid β), and activates the complement system. It causes inflammation, brain tissue degeneration and cognitive impairment, consistent with damage in AD [32]. P. gingivalis is involved in the pathogenesis of AD.

7. Porphyromonas gingivalis and the reproductive system

Studies have shown that periodontitis is associated with a variety of adverse pregnancy outcomes

(APO), such as premature rupture of membranes, preeclampsia, fetal intrauterine growth retardation, and preterm low birth weight infants [33-36].xisting evidence shows that the existence of P. gingivalis can partially explain this correlation. P. gingivalis invades periodontal or maternal-fetal tissues, causing immune environment disorder and oxidative stress in systemic and placental tissues, causing poor remodeling of uterine spiral arteries and placental vascular endothelial dysfunction leading to APO[37]. At present, there is no consensus on the source of P.gingivalis [38], and two approaches are generally recognized. (1) The ascending route through the urogenital tract reaches the placental unit. (2) It uses its own virulence factors such as fimbriae and gingivalis to adhere to and destroy periodontal tissue, and then spreads through the oral cavity to the maternal-fetal interface.

PCOS is a complex endocrine disorder characterized by anovulation, infertility, and hirsity. The pathogenesis of PCOS remains unclear. Existing evidence suggests that there may be a bidirectional association between PCOS and periodontitis (PD). The underlying molecular mechanisms of this association are not fully understood; chronic inflammation, oxidative stress, and systemic inflammation are thought to be the main causes [39]. The level of P. gingivalis in saliva of PCOS patients with periodontitis is higher [40].The subgingival biofilm composed of P. gingivalis with other bacteria triggers the activation of the host immune system, leading to the destruction of periodontal tissues due to the synthesis and release of cytokines, proinflammatory mediators, and matrix metalloproteinases. Altered periodontal responses in PCOS patients are associated with a proinflammatory state, which may increase susceptibility to periodontal disease [41]. PCOS patients are more likely to have periodontal disease than non-PCOS patients. Studies [42] showed a 28% increased risk of PD in women with PCOS and a 46% increased risk of PCOS in women with PD. The incidence of gingival bleeding, periodontal pocket depth and clinical attachment loss in PD women with PCOS was higher than that in PD women without PCOS. PCOS as a systemic endocrine disorder may affect the composition of the oral microbiota, thereby enhancing the systemic response to members of this microbiota. More studies are needed to clarify the underlying molecular mechanism.

8. Conclusion

Porphyromonas gingivalis (P. gingivalis) is the main pathogen of chronic periodontitis, which is closely related to systemic diseases. A large number of studies have confirmed that P. gingivalis exists in the lesions of diseases, but it is more crucial to find out the causal relationship between P. gingivalis and these diseases, and to conduct more prospective, multi-center and large sample studies to further explore the pathogenic molecular mechanism of P. gingivalis. It provides new ideas for the prevention and treatment of human diseases. In addition, the eradication of P. gingivalis and the timely treatment of periodontal diseases should be paid more attention. In order to improve the patients' periodontal health and quality of life, we should pay attention to periodontal health, do a good job of oral cleaning, and timely and standardized treatment of periodontal disease.

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