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Review

# Chronic Infection and Carcinogenesis: The Contribution of Porphyromonas gingivalis to Cancer Risk

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**ABSTRACT**

*Porphyromonas gingivalis* (*P. gingivalis*) is recognized as one of the most significant pathogens within the oral microbiota, which is directly associated with periodontal diseases, such as gingivitis and periodontitis. This bacterium is classified as an anaerobic, gram-negative organism. The capacity of *P. gingivalis* to produce and release various toxins further reinforces its association with numerous diseases. In recent years, the proposition of a relationship between this bacterium and certain forms of cancer has emerged. The present review aims to evaluate the existing literature that investigates the correlation between various types of cancer and *P. gingivalis*.

**Keywords:** Inflammation, cancer, *Porphyromonas gingivalis*.

*Porphyromonas gingivalis* (*P. gingivalis*), one of the most important pathogens of periodontal diseases, is a gram-negative, anaerobic bacterium that causes chronic inflammation of the gingival mucosa.[1] The dysbiosis caused by this bacterium in the oral microbiota weakens the immune system and activates carcinogenic molecular pathways, making it both a local and systemic risk.[2] In the recent past, the possible effects of *P. gingivalis* not only on the diseases caused by *P. gingivalis* in periodontal tissues but also on the development of other systemic diseases and cancers have been investigated.[3] The prominent types of these cancers are cancers related to the digestive system, oral squamous cell carcinoma, and pancreatic cancers.[4] This review aims to understand the role of *P. gingivalis* in cancer development by reviewing the literature, evaluating the mechanism, and presenting an evaluation of therapeutic approaches.

## PHENOTYPIC *PORPHYROMONAS GINGIVALIS* AND ITS CLINICAL SIGNIFICANCE

*P. gingivalis* is an important member of the oral microbiota and is a gram-negative, anaerobic bacterium.[1] Proteolytic enzymes (gingipains), capsule structures, and lipopolysaccharides are virulence factors.[5] Gingipains (Rgp, Kgp) are potent cysteine proteases produced by *P. gingivalis*. They are linked to cellular proliferation, apoptosis, and metastasis in addition to periodontal diseases.[5,6]

Gingipains play the leading role in escaping from the immune response, as well as proteolytic enzymes that trigger inflammation. Proteolytic enzymes that cause inflammation and gingipains are important for evading the immune response.[7] Gingipains are potent virulence factors that encourage the development and spread of tumors both locally (in the tissues of the mouth) and systemically.[8] They can activate cellular growth signals by targeting receptors such as epidermal growth factor receptors. This can cause cell growth.[9] Inhibiting these proteinases could be a potential technique for preventing and treating periodontal disease, as well as some malignancies.[6]

The impact on cellular proliferation is characterised by the triggering of proinflammatory cytokine secretion. Gingipains have been observed to enhance the production of proinflammatory cytokines (e.g., IL-1β and TNF-α) by disrupting proteins located on the

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cell surface. These cytokines then activate signaling pathways (e.g., NF-κB and MAPK pathways) that trigger cellular proliferation and promotion of the tumour microenvironment.[10] These cytokines can accelerate growth, especially in cancerous tissues.[11]

## ACTIVATION OF ONCOGENIC SIGNALING PATHWAY

### Suppression or Induction of Apoptosis: Anti-apoptotic Effects

Gingipains have been shown to specifically increase the expression of anti-apoptotic proteins (e.g., Bcl-2) and to suppress pro-apoptotic proteins (e.g., Bax).[6] This effect is known to prolong the lifespan of cancer cells, thereby enabling them to survive.

### Disruption of Apoptotic Mechanisms

Gingipains have been shown to cleave death receptors (e.g., FasL or TNF-α receptors) on the cell surface, thereby weakening normal apoptosis signaling mechanisms. This allows for the continuation of cellular damage and tumor formation.[11,12]

### Triggering Programmed Cell Death

It has also been reported that in some cases, gingipains can induce apoptosis by causing excessive inflammation and an increase in reactive oxygen species.[12] This phenomenon can result in the demise of healthy cells, thereby creating a favorable environment for the proliferation of cancerous cells.

## THE ROLE OF GINGIPAINS IN CANCER METASTASIS

### Degradation of Extracellular Matrix

Gingipains, a class of zinc metalloendopeptidases, have been shown to degrade extracellular matrix proteins, including collagen, fibronectin, and laminin. This process facilitates the penetration of tumor cells into surrounding tissues and blood vessels, thereby contributing to metastasis. This process marks the initial stage of metastasis.[5]

### The Encouragement of Angiogenesis

By upregulating the expression of vascular endothelial growth factors, gingipains have been shown to promote the development of new blood vessels. This procedure makes it easier for tumors to obtain oxygen and nutrients, which are essential for growth and metastasis.[8]

### Inhibition of Immune Function

It has been shown that gingipains impair the activity of immunological cells, including macrophages and T lymphocytes. This mechanism helps cancer cells avoid detection by the immune system. Consequently, metastasis is facilitated.[7]

Gingipains are potent virulence factors that promote tumorigenesis and progression at both local (e.g., periodontal tissues) and systemic levels. They are pivotal in cancer biology by enhancing cellular proliferation, modifying apoptotic pathways, and conditioning the milieu for metastasis.[6,8] Inhibiting these proteinases may provide a potential approach for the prevention and treatment of both periodontal disorders and specific cancer types.[6] *P. gingivalis* plays a pivotal role in the pathogenesis of periodontitis, a condition characterized by inflammation that results in the loss of supporting tissues and, ultimately, tooth loss.[13]

## THE RELATIONSHIP BETWEEN PERIODONTAL DISEASES AND SYSTEMIC DISEASES

Biofilm formation and bacterial dipeptidyl peptidase IV activity contribute to the pathogenicity of *P. gingivalis*. Chronic periodontitis and *P. gingivalis* are highly linked. Proinflammatory cytokines are elevated in aggressive periodontitis, led by *P. gingivalis*. The prevalence of periodontal disease is very high and is around 90% worldwide. When examining the connection between periodontal diseases and systemic diseases, it should not be forgotten that it should be examined concerning factors such as microorganisms in the biofilm, genetic and environmental factors, and tobacco use. In addition, among the diseases that may have periodontal symptoms, there are genetic, dermatological, hematological, granulomatous, immunosuppressive, and neoplastic disorders.[7,13]

## RELATIONSHIP BETWEEN INFECTION, INFLAMMATION, AND CANCER

The effect of infections on cancer is multifaceted and has micro- and macro-local and systemic micro- and macro-effects in infected tissues. Mechanisms such as chronic inflammation, immune modulation, and genetic/epigenetic changes are the cornerstones of this process. Chronic infections can trigger the development of cancer by causing constant inflammation and tissue damage.[14]

**Direct Genetic Changes**

Certain infectious agents have been observed to contribute to the development of cancer by directly damaging cellular DNA or altering genetic material.[15]

**Immune Suppression**

The immune system can be sufficiently suppressed by infections to allow the cellular alterations that characterize cancer to continue unchecked.[14]

Epstein-Barr virus has been associated with nasopharyngeal cancer and Burkitt's lymphoma. One important way that infection can lead to cancer is through the modification of immune cells by viral proteins.[16] There is a link between *Helicobacter pylori* and stomach cancer. Chronic inflammation causes mucosal metaplasia and atrophy, which can increase a person's risk of developing cancer. Certain infectious agents can contribute to carcinogenesis through direct damage to cellular DNA or alteration of genetic material.[15]

Human papillomavirus shows a strong association with cervical cancer. Tumor suppressor genes (p53 and Rb) are inhibited by the E6 and E7 proteins. According to research, infections may weaken the immune system and prevent the cellular anomalies that cause cancer from being addressed. By altering the structure of the tumor and its environment, infectious agents facilitate the growth and metastasis of cancer cells. As infections impact gene expression through the epigenetic process, these can cause carcinogenic processes. DNA methylation and histone modifications are two ways that *P. gingivalis* influences cellular alterations. Infectious substances that enter the tumor microenvironment and promote cancer cell proliferation, metastasis, and angiogenesis.[8]

Hepatitis B and C viruses cause chronic liver inflammation and cirrhosis, increasing the risk of hepatocellular carcinoma.[14]

## *PORPHYROMONAS GINGIVALIS* AND CANCER TYPES

*Oral cancer (Oral squamous cell carcinoma; OSCC)*: It can be said that *P. gingivalis*, with its presence in the oral microbiota and its pathogenicity, can increase the proliferation of epithelial cells in the oral mucosa and cause them to escape apoptosis.[17]

*Pancreatic cancer*: The association between disruption of the oral microbiota and pancreatic cancer suggests that *P. gingivalis* could be used as a biomarker for pancreatic cancer.[18]

*Gastric and colorectal cancer*: In light of the established links between chronic inflammation and immunosuppression, on the one hand, and cancer development and progression, on the other, it is hypothesized that oral *P. gingivalis* and/or virulence factors may act as an underlying mechanism between oral health and gastric carcinogenesis/gastric cancer progression.[19] It has been demonstrated that the imbalance *P. gingivalis* generates in the oral microbiota when it enters the gut microbiome sets off chronic inflammation, which could either directly or indirectly predispose people to colorectal cancer.[20]

Even in the absence of periodontitis, we can say that there is a relationship between *P. gingivalis* and cancer.[21]

*Epigenetic changes*: Inflammation and infection can trigger carcinogenic processes by altering gene expression through epigenetic pathways. Histone modifications and DNA methylation are impacted by *P. gingivalis*, which alters gene expression and ultimately contributes to cellular changes.[19]

**Methods in Clinical and Therapeutic Practices**

Treatment of periodontal disease and its potential to lower the risk of cancer, as well as the potential future role of oral microbiome-targeting therapies.[22]

Mechanisms elucidating the association between *P. gingivalis* and tumor growth promotion in cancer.[8]

In pancreatic cancer, *P. gingivalis* increases the secretion of neutrophil elastase, which speeds up the growth of tumors.[18] Constant exposure promotes the growth of OSCC by enhancing the capacity of oral epithelial cells to invade and multiply.[17]

Recent studies have also demonstrated the repercussions of *P. gingivalis* in the gastric and intestinal microenvironment. Munoz-Medel et al.[19] discovered that *P. gingivalis* promotes tumor progression by increasing the expression of immune escape genes in the gastric mucosa. Bregaint et al.[23] concluded that *P. gingivalis* outer surface vesicles in extraoral tissues increase systemic inflammation and modulate the pro-tumor microenvironment in other and distant organs. Furthermore, Motosugi et al.[20] discovered that elevated levels of *P. gingivalis* in colorectal mucosa samples were associated with an increased risk of tumor development. The detection of specific microbial DNA in saliva and faecal samples has emerged as a promising non-invasive biomarker for early diagnosis. Rocha et al.[24] concluded that the *P. gingivalis* capsule-conjugated vaccine significantly reduced alveolar bone loss by inducing a neutralizing

antibody response in mouse models of experimental periodontitis.

**Immune Modulation**

Suppression of programmed cell death factor increases cancer stem cells and chemotherapy resistance in oesophageal squamous cell carcinoma.[25]

Increasing PD-L1 expression in dendritic cells exacerbates oral cancer by suppressing CD8+ T-cell responses.[26,27]

**Chemotherapy Resistance**

Chronic *P. gingivalis* infection increases paclitaxel resistance in oral cancers, and this process depends on the inflammatory microenvironment. Co-treatment with anti-inflammatory drugs such as ibuprofen may reduce this effect.[21]

It may be possible to suppress tumor growth and improve the response to chemotherapy by concentrating on bacterial virulence factors.[9]

Immunological checkpoint blockade, B7-H4, and lysine methylase inhibitors may prevent the immunosuppressive effects of *P. gingivalis* by enhancing the immune response.[28]

**Modulation of Autophagy**

*P. gingivalis*-induced autophagy promotes cancer cell survival. Targeting this pathway may offer a therapeutic opportunity.[12]

**Vaccine Strategies**

As demonstrated in the extant literature, a vaccine targeting gingipain proteins has the potential to reduce the risk of periodontitis and associated cancers.[22,29]

In experimental models of periodontitis, the *P. gingivalis* capsule-conjugated vaccine developed by Rocha et al.[24] has been shown to significantly reduce alveolar bone loss by strongly inducing neutralizing IgG1 antibodies.

In conclusion, even though the connection between P. gingivalis and cancer appears to be at a level where we can observe it, much more research is necessary before we can draw firm conclusions about this matter and move forward with some resolution procedures. Small environmental changes in infected tissues can have both local and systemic effects, and infections can have a wide range of effects on cancer. Important mechanisms for chronic inflammation include alterations in the immune system, genetics, and all the elements required for the expression of these genes and their levels. Therapeutic modalities and new strategies targeting the P. gingivalis pathogen, including microbiome regulation, oral hygiene, and infection. We may be able to improve the results of cancer treatment through patient education and prevention.

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