

Porphyromonas Gingivalis Causing Oral Squamous Cell Carcinoma (OSCC) in Human

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ABSTRACT

While oral cancer contributes significantly to the cancer burden worldwide, oral bacteria played a key role in the spread of oral cancer. Porphyromonas gingivalis is a key pathogen for the development of periodontitis and oral squamous cell carcinoma (OSCC) in humans. The risk of developing oral cancer is enhanced with the periodontal diseases due to the inflammatory mediators and toxins released by the bacteria. The present review is an outcome of several studies done so far on P. gingivalis causing cancer to humans in the field of medical microbiology.

Abbreviations

DNA	: Deoxyribonucleic Acid
p53	: Tumor suppressor Gene
TNF	: Tumor Necrosis Factor
IL	: Interleukin
NDK	: Nucleoside Diphosphate Kinase
LPS	: Lipopolysaccharide
FimA	: Fimbriae
OSCC	: Oral Squamous Cell Carcinoma

Keywords: P. Gingivalis, Periodontitis, Biofilm, OSCC, Fimbriae, Gingipain, LPS, Acetaldehyde, Butyric Acid, Treatment

Introduction

Oral cancer has now been attracted more attention in public health worldwide due to its increasing mortality. Apart from other risk factors like alcohol consumption, chewing of tobacco and areca nuts, it has been observed that the microbial origin of cancer also played a good role in the development of oral squamous cell carcinoma (OSCC) in humans [1].

Oral Squamous Cell Carcinoma (OSCC) is the most common cancer found worldwide. The OSCC type of head and neck

cancer accounts for more than 20,000 new cases and 4,50,000 deaths in 2018 globally [2]. In 2021, nearly 54,010 new cases of OSCC were diagnosed and 10,850 patients died from OSCC only in the USA [3].

OSCC is often caused by inflammatory periodontitis. Similarly, gingivitis is a periodontal disease characterized by local inflammatory processes driven by the gingival bacteria. According to WHO, nearly 35–50% of the world's population are affected by periodontitis [4]. And globally, over 60% of all oral cancers have been reported from Asian countries like India, Pakistan, Sri Lanka and Taiwan [5] (Figure 1).

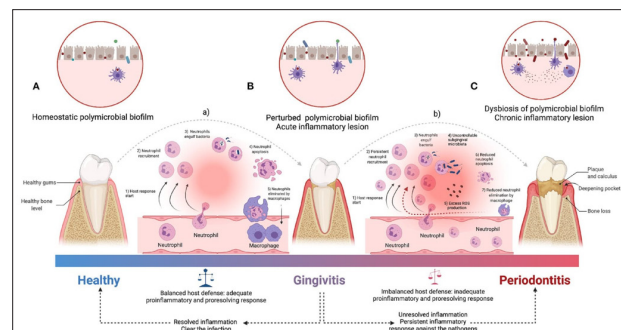


Figure 1: Pathogenesis of Periodontitis. (Photo credited from BioRender.com; Source: Martinez-Garcia and Hernandez-Lemus, 2021) [6].

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More than 700 bacterial species are found in the oral cavity of humans whose Eco balance is quite critical for maintaining a healthy physiological environment. The dysbiosis caused by them fosters the production of proinflammatory cytokines, eventually leading to the development of periodontitis. This is a kind of inflammatory disease that affects the periodontium, a gum disease that supports the teeth. To date, there are at least three bacteria mainly noted for having their crucial role in periodontitis and oral cancer in humans. They are *Porphyromonas gingivalis*, *Treponema denticola* and *Tannerella forsythia*. Out of these three, *P. gingivalis* is more ferocious in developing oral cancer in humans [4,7].

Despite several other factors, oral cancer caused by bacterial dysbiosis has been recently discovered with a lot more evidence about the carcinogenicity of *Porphyromonas gingivalis*. It activates several oncogenic pathways to assist OSCC development. It also inhibits apoptosis of gingival cells [8]. (Figure 2).

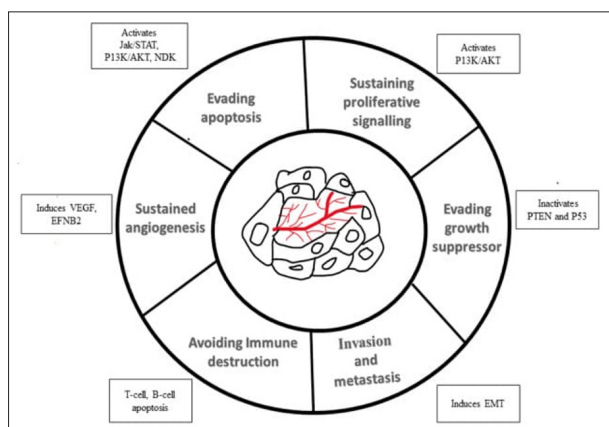


Figure 2: Signals Derived from *Porphyromonas gingivalis* Influencing Multiple Hallmarks of Cancer Via a Variety of Mechanisms [8].

To date, a good amount of research has allowed us to understand the bacterial origin of cancer; however, more studies are still required to determine the combined effect of oral species in carcinogenesis. The present paper deals with the study of major mechanisms involved in periodontitis caused by *Porphyromonas gingivalis* and the development of oral squamous cell carcinoma in humans.

Mechanism of Cancer Development

P. gingivalis, originally found in the human oral cavity, is sometimes associated with an increased risk of oral squamous cell carcinoma and gastrointestinal cancers [9]. This is carried out with the help of various virulence factors like fimbriae (FimA), cysteine proteases (gingipains), lipopolysaccharide (LPS) and nucleoside diphosphate kinase (NDK) [10].

P. gingivalis, by its two types of fimbriae, assists in cell invasion. These two types are Fimbrillin (FimA) and Mfa1, found on the surface of the cell. They invade the gum tissues, developing chronic inflammation by producing cytokines like IL-1, IL-6, IL-8 and TNF- α [11]. (Figure 3)

Similarly, gingipain is required for the maturation of fimbriae (FimA). It also performs a variety of functions like epithelial

cell adherence and invasion, erythrocyte hemagglutination and hemolysis, inflammatory reaction and host protein degradation. Gingipain is a trypsin-like cysteine proteinase enzyme [13].

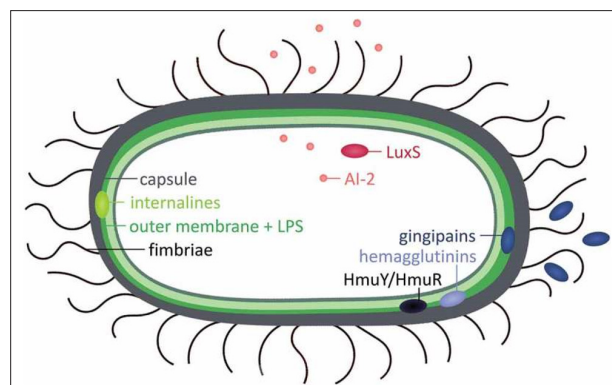


Figure 3: Determinants Involved in Biofilm Formation of *Porphyromonas gingivalis* [12].

While *P. gingivalis* LPS disrupts the immunity system of the host cell, NDK hinders apoptosis [14].

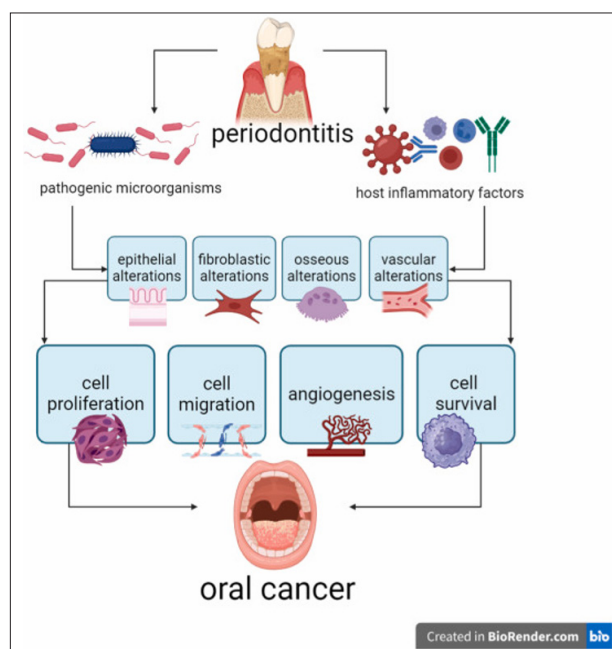


Figure 4: Major Mechanisms involved in Periodontitis and the Development of Oral Squamous Cell Carcinoma (OSCC) [15].

In fact, the bacteria develop cancer in humans by interrupting apoptosis and producing carcinogenic compounds, causing chronic inflammation [16].

Acetaldehyde and butyric acid are the two metabolites produced by *P. gingivalis*, causing DNA damage, mutation and cell proliferation. The bacterium finally produces oral squamous cell carcinoma (OSCC) by altering the tumor suppressor gene p53 [17-19] (Figure 4).

Recurrence and Prognosis of Oral Cancer

Porphyromonas gingivalis activation of tumor-associated macrophages via DOK3 promotes recurrence of oral squamous cell carcinoma. OSCC is characterized by its high recurrence rate with poor prognosis. Approximately, 4 lakhs new cases every year have been diagnosed worldwide, accounting for

2% of all cancers. The poor prognosis of OSCC may be due to the bacterial strong invasive ability, high recurrence rate and metastasis of lymph nodes [20,21].

Treatment of P. Gingivalis-Induced OSCC

Traditionally, OSCC has still been treated by excision therapy and surgery, radiation and chemotherapy [22-24]. But it has been observed that OSCC developed by Porphyromonas gingivalis has got tremendous radio resistance, chemoresistance and immune suppression. However, currently certain emerging therapeutic strategies are being applied for the treatment of OSCC including biomimetic nano therapy, immunological targeting, metabolic and stemness inhibition and signaling and metastasis interruption. Targeted delivery systems have also been developed using photochemical ablation and localized antibiotic release to kill the intracellular bacteria [12, 25-28].

Conclusion

Currently, it has been observed that oral microbial dysbiosis causes microbial flora imbalance and chronic inflammation, developing OSCC in humans. The microbial release of toxins and metabolites disrupts the immune system to produce OSCC. However, simply the presence of these species does not necessarily mean to produce cancer. The dysbiosis of oral microbiota with the dominance of any particular oncogenic species in huge amounts in Eco disturbance might cause cancers in future. They produce nitrosamines and procarcinogens for the development of oral cancer. Most specifically, in the case of Porphyromonas gingivalis, the inhibition of apoptosis or programmed cell death takes place. Further, inflammatory cytokines are released, accelerating intracellular inflammation and cancer. It also alters and reduces the activity of the p53 tumor suppressor gene [1,15].

Oral cancer, ranking sixth among the most common cancers worldwide, OSCC covers nearly 90% of all cases [29]. OSCC has been found to be linked with the carcinogenicity of oral microbes. It has now become a big problem worldwide and, despite all the clinical facilities provided to the patients in the past few decades, the five-year survival rate is not improved significantly. This is a primary common oral cancer with poor prognosis and a median overall survival of 5 years in only 50–60% of patients. Contemporary standard treatment is still composed of radiotherapy and chemotherapy. However, OSCC induced by P. gingivalis has been found to be radioresistant and/or chemoresistant. Several emerging therapeutic strategies are being explored for the treatment of OSCC in humans.

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