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The Interplay of Oral Microbiome, Chronic Inflammation, and Periodontitis in Oral Carcinogenesis

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Abstract

Chronic inflammation plays a pivotal role in carcinogenesis, with the oral cavity representing a key site where microbial dysbiosis and host immune responses interact to promote tumor development. Periodontitis, a persistent inflammatory disease driven by pathogenic bacteria such as *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, and *Tannerella forsythia*, contributes to the destruction of periodontal tissues and may facilitate cancer initiation and progression. Epidemiological and molecular evidence links periodontal pathogens to various malignancies, including oral, gastrointestinal, and pancreatic cancers, as well as non-Hodgkin lymphoma. Microbial-driven carcinogenesis involves multiple mechanisms, including acetaldehyde production, nitrate-to-nitrite conversion, and enhanced penetration of environmental carcinogens into inflamed tissues. Periodontal tumors, whether benign or malignant, require early detection, accurate diagnosis, and appropriate treatment to prevent functional and aesthetic complications. Recognizing periodontitis as a modifiable risk factor underscores the importance of maintaining oral microbial balance and implementing effective periodontal therapy as potential strategies for cancer prevention. Further studies are necessary to clarify molecular pathways and develop targeted interventions.

Keywords: Periodontitis; Oral microbiome; Oral cancer; Chronic inflammation; Carcinogenesis; Periodontal tumors; *Porphyromonas gingivalis*; *Aggregatibacter actinomycetemcomitans*; Microbial dysbiosis; Cancer prevention

Introduction

Chronic inflammation has long been recognized as a contributing factor to carcinogenesis. Rudolf Virchow was the first to suggest a possible link between inflammation and cancer in the 19th century, noting leukocyte infiltration within tumor microenvironments and hypothesizing that persistent inflammation might drive tumor development [1]. In the head and neck region, genetic alterations induced by external factors such as tobacco use, alcohol consumption, and ultraviolet radiation promote carcinogenesis [2]. Increasing evidence highlights the role of microorganisms, particularly within the oral cavity, in modulating inflammation and influencing tumorigenesis [3-5]. This review aims to elucidate the complex interactions between the oral microbiome, periodontitis, and oral cancer, emphasizing pathogenic mechanisms and clinical implications.

Development

Periodontal Tumors and Classification

Periodontal tumors comprise abnormal proliferations of the tissues surrounding the teeth. These lesions may be benign or malignant, with early diagnosis being paramount for effective management. Common benign tumors include fibromas and pyogenic granu-

lomas, while malignant tumors primarily consist of squamous cell carcinomas and sarcomas [6-9].

In-depth knowledge of periodontal lesions is essential for the professional practice of dentistry. Dentists must remain constantly updated, develop skills to perform accurate differential diagnoses of the various pathological conditions that may occur in, or originate from, the periodontium, and be proficient in the different treatment modalities—pharmacological, surgical, and conservative—as well as in the management of potential complications.

Periodontal lesions may arise from multiple causes, including infectious, tumorous, and even traumatic processes. Timely identification and appropriate management of these conditions are crucial to preserving oral health and preventing functional or aesthetic sequelae (see Figures 1, 2, and 3).

Figure 1: See in Risks and Complications in Fungal Infections.

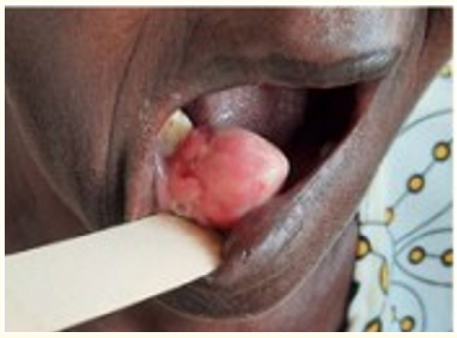

Figure 2: See in Risks and Complications in Tumors of Odontogenic Origin.

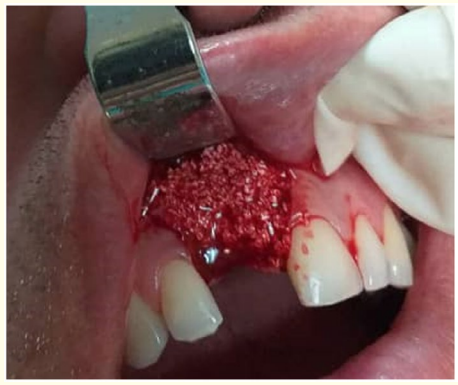

Figure 3: Patient who underwent guided bone regeneration following a dental extraction due to traumatic periodontal disease.

Pathophysiology Linking Periodontitis and Cancer

Periodontitis is a chronic inflammatory condition resulting from dysbiotic oral microbiota, characterized by destruction of periodontal ligament and alveolar bone. The chronic inflammation observed in periodontitis promotes DNA damage and facilitates tumorigenesis [1, 4]. Key periodontal pathogens, including *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, and *Tannerella forsythia*, have been identified as etiologic agents that sustain inflammation and potentially contribute to carcinogenesis [8, 9].

Oral Microbiome in Disease Modulation

The oral microbiome, first identified by Antony van Leeuwenhoek in the 17th century [6], plays a crucial role in maintaining oral homeostasis and modulating immune responses [5, 6]. Dysbiosis of the oral microbiota underlies the pathogenesis of periodontitis and has been implicated in systemic autoimmune conditions such as type 1 diabetes and rheumatoid arthritis [10].

Epidemiological and molecular studies demonstrate associations between periodontal pathogens and increased risk of various cancers. For example, *A. actinomycetemcomitans* correlates with precancerous gastric lesions, whereas *Fusobacterium nucleatum* and Bacteroides species associate with colorectal cancer and appendicitis [11-13]. The oral microbiome composition varies among cancer types; *Treponema denticola*, *Streptococcus mitis*, and *Streptococcus anginosus* predominate in esophageal cancers, while *F. nucleatum* is abundant in colorectal malignancies [13].

P. gingivalis and *F. nucleatum* have been detected in multiple cancers of the gastrointestinal tract and pancreas [14-17]. Moreover, periodontal disease has been linked to non-Hodgkin lymphoma, with tooth loss showing an inverse association with NHL possibly due to reduced local oral inflammation [18]. Tooth loss is considered a risk marker rather than a causal factor in esophageal cancer [19, 20]. Periodontal bone loss has also been implicated in oral cancer risk [21].

Oral streptococci (*S. intermedius*, *S. constellatus*, *S. oralis*, *S. mitis*, *S. sanguis*, and *S. salivarius*) have been isolated from cervical lymph nodes of oral cancer patients, suggesting microbial translocation or involvement in tumor progression [22]. The bacterium Helicobacter pylori has been associated with both periodontitis and oral cancer, highlighting a possible infectious link [18, 23, 24].

Mechanisms of Microbial-Driven Carcinogenesis

Alcohol metabolism by the oral microbiota generates acetaldehyde, a recognized carcinogen that contributes to head and neck cancer risk. Periodontal bacteria convert nitrates to nitrites and produce acetaldehyde, both implicated as carcinogenic metabolites. Tobacco and alcohol-derived carcinogens penetrate periodontal tissues compromised by inflammation, potentially accelerating tumorigenesis. The oral microbiome may influence carcinogenesis through multiple signaling pathways, although the exact molecular mechanisms remain under investigation.

Conclusions

Emerging evidence underscores the critical role of the oral microbiome and chronic periodontal inflammation in the pathogenesis of oral and systemic cancers. The interplay between specific periodontal pathogens, host immune responses, and environmental carcinogens contributes to tumor initiation and progression. Periodontitis should be recognized not only as a local inflammatory disease but also as a potential modifiable risk factor for various malignancies, particularly oral cancer. Early diagnosis, effective periodontal therapy, and maintaining oral microbial balance may represent important strategies for cancer prevention. Further research is warranted to elucidate precise molecular mechanisms and to develop targeted interventions.

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