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Review

Role of oral microbiome on oral cancers, a review

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ABSTRACT

The oral cavity is inhibited by many of the bacterial species. Some of them have a key role in the development of oral disease. Interrelationships between oral microbiome and systemic conditions such as head-and-neck cancer have become increasingly appreciated in recent years. Emerging evidence also suggests a link between periodontal disease and oral cancer, and the explanation being that chronic inflammation could be a major factor in both diseases. Squamous cell carcinoma is that the most frequently occurring malignancy of the oral cavity and adjacent sites, representing over 90% of all cancers. The incidence of oral cancer is increasing, significantly among young people and women. Worldwide there are 350,000–400,000 new cases diagnosed every year. Bacteria, viruses, and fungi are strongly implicated as etiological factors in certain cancers. In this review we will discuss the association between the development of oral cancer in potentially malignant oral lesions with chronic periodontitis, chronic *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, candida, other microbes and described mechanisms which may be involved in these carcinoma.

Contents

1. Introduction

The oral microbiome plays an essential role within the maintenance of a normal oral physiological environment. They play a role in development of oral diseases, such as, periodontal disease and tooth loss [1,2]. Although little studied, the oral microbiome could also be important in cancer and other chronic diseases, through direct metabolism of chemical carcinogens and general inflammatory effects [3]. A role for bacterial infection in inflicting or promoting cancer is renowned with relevancy to the association of *Helicobacter pylori* with gastric cancer [4]. Other cancers, such as, colon, gallbladder, prostate and lung, have been associated with particular bacterial infections [5,6]. The oral cavity is home to a various microbial community of more than 700 microbial species as well as commensal and opportunistic bacterium, fungi and viruses. They are living in a symbiotic relationship with one another and the host immune system [7,8].

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Deregulated host immune responses ensuring from environmental and systemic exposures (e.g., obesity, smoking, diabetes, aging, stress), host genetic, and epigenetic defects. Dysbiotic oral microflora subvert the host defense mechanisms result in chronic periodontal disease [9,10]. It is reasonable to ask, therefore, if shifts within the composition of the normal oral cavity microbiome, comprised of more than 600 different bacterial species [11]. Also chronic bacterial infection might be promoters or causes of oral cancer. Indeed, changes within the microbial community are commonly related to dental diseases like periodontitis, that is possibly a polymicrobial disease characterized by outgrowth of certain pathologic organisms [12]. Chronic periodontal disease has been reported to be a risk factor for oral premalignant lesions and cancers [13]. Emerging evidence also suggests a link between periodontal disease and oral cancer. The explanation being that chronic inflammation could be a major factor in periodontitis and oral cancer [14,15]. The development and progression of periodontal disease could be a complex process initiated by a dysbiotic polymicrobial insult. This complex process involves multiple host cells of myeloid and non-myeloid origin such as neutrophil polymorphs (PMNs), oral keratinocytes, monocytes, macrophages, osteoblasts, osteoclasts and dendritic cells. These cells possess cytosolic, membrane-associated receptors, and secreted pattern recognition receptors (PRRs) as well as NOD-like receptors (Nucleotide-binding Oligomerization Domain, NLRs), toll-like receptors (TLRs), RIG-I-like receptors (RLR), and C- type lectin receptors. They may intract with periodontal microbial associated molecular patterns (MAMPs) [e.g., fimbriae, BspA (*Bacteroides* surface protein A), lipoproteins, lipopolysaccharide (LPS), nucleic acids] and damage/danger associated molecular patterns (DAMPs) (e.g., fibrinogen, heat-shock proteins, nucleic acids) [16]. Squamous cell carcinoma is that the most frequently occurring malignancy of the oral cavity and adjacent sites, representing over 90% of all cancers. Worldwide, 200,000 new cases of oral cavity and lip cancer are diagnosed every year, with around 98,000 deaths (http://globocan.iarc.fr/Pages/fact_sheets_population.aspx). The incidence of oral cancer is increasing, significantly among young people and women. Worldwide there are 350,000–400,000 new cases diagnosed every year [17,18]. The predominant risk factors for oral cavity cancer are tobacco and alcohol use. The carcinogens impact on the oral mucosa to form a field that's susceptible to undergo malignant transformation, so-called "field cancerization" [19]. The foremost risk factors, alcohol and tobacco use, cannot explain the changes in incidence, as a result of oral cancer also commonly occurs in patients while not a history of alcohol or tobacco exposure [20]. Recently, human papillomavirus (HPV) has been known as an etiologic agent for oropharyngeal cancer, however HPV infection isn't a major contributor to oral cancer, because the virus is rarely found in these cancers (2–4% of cases) [21]. The molecular pathogenesis of oral cavity cancer is, in several cases, the results of dysregulation of common signaling pathways that actively drive oncogenesis, on a background of tumor suppressor inactivation. The basis for this could be a mixture of somatic mutations, as represented recently [22], along with transcriptomic alterations and epigenetic. Inactivation of the P53 and CDKN2A tumor suppressors additionally happens with high frequency in oral cancer. Additionally to molecular dysregulation as a results of chemical carcinogens in alcohol and tobacco, infectious agents play a significantly role in development and progression of oral cancer. Though significantly less frequent than within the oropharynx, human papilloma viral related carcinogenesis contributes to a little proportion of oral cavity cancers [around 10%] [22].

2. Periodontitis

The oral cavity is liable to variety of bacterial infectious diseases, like periodontal disease. Periodontal disease is potential that oral bacterium might serve to initiate or promote tumor development, analogous to the association of gastric cancer with *Helicobacter pylori* infection. In fact, variety of periodontal bacteria such as *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Prevotella intermedia*, are related to oral squamous cell carcinoma (OSCC) [23,24]. Mager et al. suggested that high salivary counts of *Prevotella melaninogenica*, *Streptococcus mitis* and *Capnocytophaga gingivalis* could also be diagnostic indicators of OSCC [23]. These findings taken with those of associate earlier study indicate that the presence of an OSCC features a more powerful impact on the salivary microbiota than either periodontitis or smoking. Instead oral microbiome might have a direct or indirect role in oral carcinogenesis. Some oral microbiome biotypes might contribute more to carcinogenesis than others. Arguments for and against these prospects are going to be designed below:

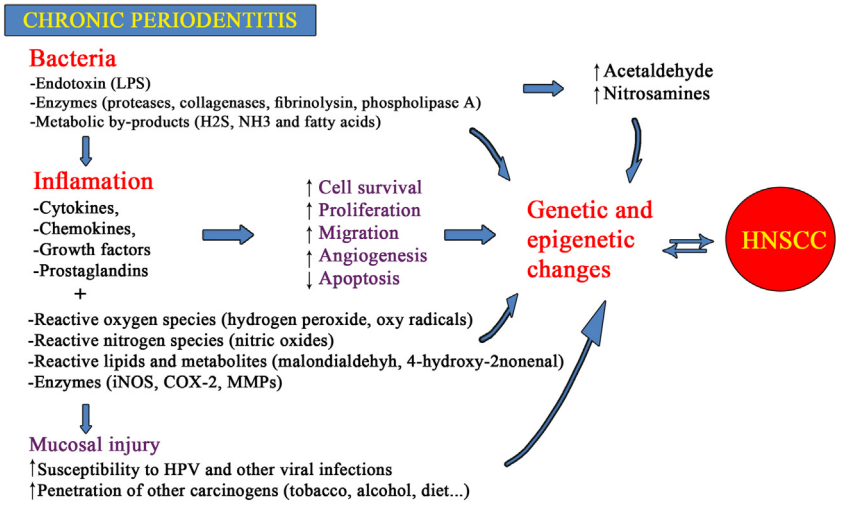

Fig. 1. A model for the role of chronic periodontal disease in head-and-neck cancer [30]. Enzymes, endotoxin and metabolic by-products of bacteria could be induced to secrete some inflammation substances from squamous cells, such as cytokines, which may act on the cells. Cytokines effect on cells may decrease apoptosis pathway and cell survival can be increased. This factors together multiple toxic components, which in turn may cause genetic and epigenetic changes and mucosal injury. Over time, all above-mentioned processes can cause head-and-neck squamous cell carcinoma.