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Research Article

UNLOCKING OF PERIO PATHOGENIC BACTERIA'S CABINET OF CURIOSITIES IN ORAL CARCINOGENESIS

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A B S T R A C T

Oral cancer is considered as one of the most common cancer diagnosed in Indian population and is known as leading cause of cancer deaths. It is considered as a multifactorial disease because apart from genetic mutations and risk factors like smoking, various other carcinogens are also involved. The role of viruses in carcinogenesis has been well studied and documented. However, the role of microbiota of oral cavity, in particular perio pathogenic bacteria like Porphyromonas gingivalis and Fusobacterium nucleatum, in carcinogenesis is still weak. The upregulation of cytokines, inflammatory mediators and release of toxic products by these bacteria all affect the complex metabolic pathways which may thus be involved in carcinogenesis. Therefore, this review explores association of perio pathogenic bacteria in oral carcinogenesis.

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INTRODUCTION

Oral cancer, primarily oral squamous cell carcinoma (OSCC), continues to be a major health problem with high incidence and low survival rates. Although lifestyle factors have been identified as major risk factors for this type of malignancy, around 15% of oral cancer cases remain unexplained.[1] To explore this unexplained cause, several epidemiological studies have been conducted to assess the possible role of bacteria in OSCC as human mouth conceals one of the most diverse microbiota.

A triad of oral anaerobic bacteria that comprises *Porphyromonasgingivalis*, *Treponemadenticola* and *Tannerella forsythia* have traditionally been considered as causative agents of periodontitis, based on their virulence properties and strong association with diseased sites.[2] *This* disease results not from individual pathogens but rather from polymicrobial synergy and dysbiosis, which disturb the eco-logically balanced biofilm associated with periodontal tissue homeostasis.[3-5] The dysbiosis of the periodontal microbiota cause pathogenic entity that can result in disease of oral or extra-oral tissues in susceptible individuals.[6] There has been increasing evidence suggesting that the establishment of a variety of chronic diseases could result from polymicrobial interactions within the underlying microbiome, harmonious with host genetic and metabolic risk factors.[7-9]

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Therefore, this review provides analysis of unexplored association of perio-pathogenic bacteria in oral carcinogenesis.

Healthy Oral Microbiome

Oral cavity harbours several distinct niches that provide unique conditions and nutrients for populating microbes, predominately bacteria.[10] Each niche displays site specificity and distinct bacterial profile.[11] Once established, the oral microbial communities maintain a stable composition 'microbial homeostasis'.[12] The host provides its microbial communities with an environment where they can flourish; in return, microbes protect the host as they colonize specific surfaces and prevent adherence and/or hinder growth of pathogenic bacteria.[13]

Oral Microbial Dysbiosis in Periodontal Disease

The changeover from periodontal health to disease is associated with a dramatic shift from a symbiotic microbial community which is composed mostly of facultative bacteria genera to a dysbiotic microbial community that is composed of anaerobic genera. Subsequently, these pathogens become capable of causing diseases within and beyond the oral cavity. A variety of periodontal bacteria such as Porphyromonas gingivalis, Fusobacterium nucleatumare related to OSCC.[14, 15]

Currently, there is increasing interest in the possible role of microbial dysbiosis in cancers.

It has been reported that each millimeter of alveolar bone loss is associated with a 5.23-fold increase in the risk of tongue cancer[16] and with more than a 4-fold increase in the risk of

head and neck squamous cell carcinoma (HNSCC) such as oropharyngeal and laryngeal carcinomas.[17] This association between periodontal disease and HNSCC is remarkable even in nonsmokers, making periodontal disease an independent risk factor for HNSCC.[17] In addition, it has been indicated that patients with periodontitis are more likely to develop poorly differentiated OSCC than those without [17], showing the association of periodontal disease with the development as well as progression of oral cancer.

Oral Microbial Dysbiosis in Oral Cancer

High levels of *Porphyromonas spp., Fusobacterium spp*. and other bacterial species were significantly higher on OSCC tissue compared with adjacent healthy mucosa.[14]

Among the first studies to examine association between periodontitis and cancer was a case–control study conducted between 1999 and 2005 in the USA that examined 473 patients.[17] It was seen that chronic periodontitis was associated with four-fold increase in risk of any of the three examined types of carcinoma, squamous cell carcinoma of the oral cavity, pharynx and larynx. The strength of the association was greatest with cancers of the oral cavity, followed by cancers of oropharynx and larynx. It should be noted that the association persisted in subjects who never used tobacco and alcohol, which suggests that chronic periodontitis is an independent risk factor for the development of cancer.[17]

In National Health and Nutrition Examination Survey III, potential link between *P. gingivalis* and orodigestive cancers were noticed.[18] Moderate or severe periodontitis was found to be associated with an increased relative risk for mortality in orodigestive cancer. The highest association with periodontitis was found for colorectal and pancreatic cancer, whereas greater serum *P. gingivalis* IgG levels tended to be associated with increased orodigestive cancer mortality.[18]

Interestingly, *P. gingivalis* was also associated with 2.25-fold higher likelihood of orodigestive mortality in healthy subjects not exhibiting overt periodontal disease pinpointing that *P. gingivalis* could be a valuable biomarker for microbe-associated risk of orodigestive cancer death.[18]

P. gingivalis was detected in the samples of submandibular and submental lymph nodes of approximately 20% of patients with histories of head and neck cancers, including OSCC and it was suggested that the translocation of periodontopathic bacteria may occur via lymphatic drainage, irrespective of cancer disease status or therapy.[19]

Significant increase of *P. gingivalis* strains in OSCC tissues than normal tissues were highlighted for the first time by analyzing oral tissue samples.[20]

Higher levels of periodontopathic bacteria like *P. gingivalis*, *A. actinomycetemcomitans* and *T. denticola* colonization were seen in plaque and saliva samples in the patients with intestinal metaplasia or dysplasia suggesting an increased risk of gastric pre-cancerous lesions in individuals with periodontal disease.[21]

Role of Periopathogenic Bacteria in Oral Carcinogenesis

Inhibition of Apoptosis

P. gingivalis stimulates JAK1/STAT3 and PI3K/Akt signaling which are described as key regulators of cellular processes that can lead to initiation and/or maintenance of carcinogenesis and controls intrinsic mitochondrial apoptosis pathways.[22,23] Furthermore, *P. gingivalis* also secretes a nucleoside diphosphate kinase (NDK), which prevents ATP-dependent apoptosis mediated through purinergic receptor P2X7 on gingival epithelial cells.[24]

The ATP-coupled P2X7 signaling has direct implications for the regulation of a variety of specific host immune response elements that were recently shown to be critically involved in the pathways favoring carcinogenesis.[25-27]

Activation of Cell Proliferation

The studies with the human primary oral epithelial cells revealed that *P. gingivalis* infection accelerates the progression through the S-phase of the cell cycle via the modulation of pathways involving cyclins and p53.[24,28] The infection by the organism *P. gingivalis* is also known to alter the expression of 'p53 tumor suppressor', which is known to be involved in the DNA damage response and in tumor suppression.[29] Actions of *P. gingivalis* appeared to be dependent on the presence of the major fimbriae (FimA) of the organism.[28]

In human epithelial cells, infection by *F. nucleatum*alsoresults in the upregulation of 12 kinases, the majority of which are involved in cell proliferation and cell survival signalling as well as DNA repair.[30]

Promoting Cellular Migration and Invasion

P. gingivalis and *F. nucleatum* promote cellular invasion in OSCC. Using an OSCC cell line, *P. gingivalis* infection was demonstrated to upregulate expression of pro-matrix metalloproteinase-9 (pro-MMP-9) by the activation of the ERK1/2-ETS1, p38/HSP27 and PAR/ NF-kB pathways; gingipains then cleave the proenzyme into active MMP-9, enhancing the cellular invasion.[31, 32]
Repeated exposure to *P. gingivalis* can also increase invasiveness of OSCC cells by triggering epithelial to mesenchymal transition (EMT) and enhanced production of MMP-1 and MMP-10.[33]

In a similar fashion, the infection of human epithelial cells by *F. nucleatum* increases the production of MMP- 13 (collagenase 3) through the activation of mitogen activated protein kinase p38 and promotes cellular migration.[30]

Induction of Inflammation

Chronic inflammation, triggered by infections or environmental exposures, plays a pivotal role in all the stages of carcinogenesis including induction, progression, invasion and metastasis.[34] Reactive oxygen species (ROS), reactive nitrogen intermediates (RNI) and cytokines produced by inflammatory cells are believed to contribute to the initiation of cancer by inducing mutations, genomic instability and epigenetic alterations. Inflammatory cytokines which are released then activate the key transcription factors such as STAT3 and NF-kB within the premalignant cells; this in turn supports pro-malignant processes including proliferation, angiogenesis, and invasion and metastasis, and most importantly, results in a sustained tumour-promoting inflammation within the tumour microenvironment.[34,35] Therefore, chronic inflammation provides a plausible explanation for the strong association between periodontitis and a higher risk of OSCC.[36]

Production of Carcinogens

Certain bacteria and Candida spp. in the oral cavity possess the enzyme alcohol dehydrogenase (ADH), which catalyses the production of mutagenic amounts of acetaldehyde under aerobic or microaerophilic conditions.[37,38-40] The International Agency for Research on Cancer classified acetaldehyde associated with alcohol consumption as a Group 1 carcinogen in humans, with the capability to cause sister chromatid exchanges, point mutations and hyper proliferation of epithelium.[41,42] Examples of oral bacteria include *S. salivarius, S. intermedius, S. mitis*[43] and nonpathogenic *Neisseria spp.*[44]

CONCLUSION

In summary, oral mucosa harbors an enormous amount of naturally occurring microbes on the epithelial surfaces, which have a direct effect on the occurrence and or advancement of precancerous and cancerous formations in the oral cavity. The association of *P. gingivalis* to orodigestive cancer is still questionable, however, recent findings suggest that the organism is perhaps an important predisposing factor that directs the development or poor prognosis of orodigestive cancers and possibly other chronic diseases.

Future large-scale integrated clinical studies accompanied by in vivo assays may determine the specific microbial components and the associated microbiome populations that may well participate in cancer and the complex bacteria–host interaction contributing to these devastating chronic diseases. Therefore, in order to reduce oral microbial load, a thorough periodontal therapy is mandatory. Thus, any suspicious cases of oral cancer needs to be treated with multidisciplinary therapy with periodic periodontal visits.

References

1. Noureen C, Pankaj C, Rushikesh D. The role of bacteria in oral cancer. *Indian J Med PaediatrOncol*. 2010; 31:126-31.
2. Socransky SS, Haffajee AD. Periodontal microbial ecology. *Periodontol* 2000. 2005; 38:135-87.
3. Darveau RP. Periodontitis: a polymicrobial disruption of host homeostasis. *Nature Rev Microbiol* 2010;8:481-90.
4. Rosier BT, De Jager M, Zaura E, Krom BP. Historical and contemporary hypotheses on the development of oral diseases: are we there yet? *Front* Cell *Infect Microbiol* 2014;4.
5. Hajishengallis G, Lamont RJ. Beyond the red complex and into more complexity: the polymicrobial synergy and dysbiosis (PSD) model of periodontal disease etiology. *Mol Oral Microbiol* 2012; 27:409-19.
6. Kebschull Á, Demmer RT, Papapanou PN. "Gum bug, leave my heart alone!"—epidemiologic and mechanistic evidence linking periodontal infections and atherosclerosis.*J Dent Res* 2010; 89:879-902.
7. Wroblewski LE, Peek RM, Wilson KT. Helicobacter pylori and gastric cancer: factors that modulate disease risk.*ClinMicrobiol Rev* 2010; 23:713-39.
8. Sheh A, Fox JG. The role of the gastrointestinal microbiome in Helicobacter pylori pathogenesis. *Gut microbes*. 2013; 4:505-31.
9. Michaud DS. Role of bacterial infections in pancreatic cancer. *Carcinogenesis*. 2013; 34:2193-7.
10. Dewhirst FE, Chen T, Izard J, Paster BJ, Tanner AC, Yu WH, Lakshmanan A, Wade WG. The human oral microbiome.*J Bacteriol* 2010; 192:5002-17.
11. Aas JA, Paster BJ, Stokes LN, Olsen I, Dewhirst FE. Defining the normal bacterial flora of the oral cavity.*J ClinMicrobiol* 2005; 43:5721-32.
12. Do T, Devine D, Marsh PD. Oral biofilms: molecular analysis, challenges, and future prospects in dental diagnostics. *ClinCosmetInvestig Dent* 2013;5:11.
13. Zarco MF, Vess TJ, Ginsburg GS. The oral microbiome in health and disease and the potential impact on personalized dental medicine.*Oral Dis* 2012; 18:109-20.
14. Nagy KN, Sonkodi I, Szöke I, Nagy E, Newman HN. The microflora associated with human oral carcinomas.*Oral Oncol* 1998; 34:304-8.
15. Katz J, Onate MD, Pauley KM, Bhattacharyya I, Cha S. Presence of Porphyromonasgingivalis in gingival squamous cell carcinoma. *Int J Dent Oral Sci* 2011; 3:209.
16. Tezal M, Sullivan MA, Reid ME, Marshall JR, Hyland A, Loree T, Lillis C, Hauck L, Wactawski-Wende J, Scannapieco FA. Chronic periodontitis and the risk of tongue cancer.*Arch Otolaryngol Head Neck Surg* 2007; 133:450-4.
17. Tezal M, Sullivan MA, Hyland A, Marshall JR, Stoler D, Reid ME, Loree TR, Rigual NR, Merzianu M, Hauck L, Lillis C. Chronic periodontitis and the incidence of head and neck squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev* 2009; 18:2406-12.
18. Ahn J, Segers S, Hayes RB. Periodontal disease, Porphyromonas g ingivalis serum antibody levels and orodigestive cancer mortality. *Carcinogenesis*. 2012; 33:1055-8.
19. Rajakaruna GA, Umeda M, Uchida K, Furukawa A, Yuan B, Suzuki Y, Noriko E, Izumi Y, Eishi Y. Possible translocation of periodontal pathogens into the lymph nodes draining the oral cavity. *Int J Microbiol* 2012; 50:827-36.
20. Katz J, Onate MD, Pauley KM, Bhattacharyya I, Cha S. Presence of Porphyromonasgingivalis in gingival squamous cell carcinoma. *Int J Dent Oral* Sci2011; 3:209.
21. Salazar CR, Sun J, Li Y, Francois F, Corby P, Perez-Perez G, Dasanayake A, Pei Z, Chen Y. Association between selected oral pathogens and gastric precancerous lesions. PloS one. 2013; 8:e51604.
22. Yilmaz Ö, Jungas T, Verbeke P, Ojcius DM. Activation of the phosphatidylinositol 3-kinase/Akt pathway contributes to survival of primary epithelial cells infected with the periodontal pathogen Porphyromonasgingivalis. *Infect Immun* 2004; 72:3743-51.
23. Mao S, Park Y, Hasegawa Y, Tribble GD, James CE, Handfield M, Stavropoulos MF, Yilmaz Ö, Lamont RJ. Intrinsic apoptotic pathways of gingival epithelial cells modulated by Porphyromonasgingivalis. *Cell Microbiol* 2007; 9:1997-2007.
24. Yilmaz Ö, Yao L, Maeda K, Rose TM, Lewis EL, Duman M, Lamont RJ, Ojcius DM. ATP scavenging by the intracellular pathogen Porphyromonasgingivalis inhibits P2X7-mediated host-cell apoptosis. *Cell Microbiol* 2008; 10:863-75.

25. Roger S, Pelegrin P. P2X7 receptor antagonism in the treatment of cancers. *Expert OpinInvestig Drugs*2011; 20:875-80.
26. Adinolfi E, Amoroso F, Giuliani AL. P2X7 receptor function in bone-related cancer.*J Osteoporos* 2012.
27. Di Virgilio F. Purines, purinergic receptors, and cancer.*Cancer Res* 2012; 72:5441-7.
28. Kuboniwa M, Hasegawa Y, Mao S, Shizukuishi S, Amano A, Lamont RJ, Yilmaz O. P. gingivalis accelerates gingival epithelial cell progression through the cell cycle. *Microbes Infect* 2008; 10:122-8.
29. Ozaki T, Nakagawara A, Nagase H. RUNX family participates in the regulation of p53-dependent DNA damage response.*Int J Genomics*. 2013.
30. Uitto VJ, Baillie D, Wu Q, Gendron R, Grenier D, Putnins EE, Kanervo A, Firth JD. Fusobacterium nucleatum increases collagenase 3 production and migration of epithelial cells.*Infect Immun* 2005; 73:1171-9.
31. Rubinstein MR, Wang X, Liu W, Hao Y, Cai G, Han YW. Fusobacterium nucleatum promotes colorectal carcinogenesis by modulating E-cadherin/β-catenin signaling via its FadAadhesin. *Cell host & microbe* 2013; 14:195-206.
32. Inaba H, Sugita H, Kuboniwa M, Iwai S, Hamada M, Noda T, Morisaki I, Lamont RJ, Amano A. Porphyromonasgingivalis promotes invasion of oral squamous cell carcinoma through induction of proMMP9 and its activation.*Cell Microbiol* 2014; 16:131-45.
33. Ha NH, Woo BH, Ha ES, Choi JI, Kim SJ, Park BS, Lee JH, Park HR. Prolonged and repetitive exposure to Porphyromonasgingivalis increases aggressiveness of oral cancer cells by promoting acquisition of cancer stem cell properties.*Tumour*Biol 2015; 36:9947-60.
34. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell* 2010; 140:883-99.
35. Landskron G, De la Fuente M, Thuwajit P, Thuwajit C, Hermoso MA. Chronic inflammation and cytokines in the tumor microenvironment. *J ImmunolRes* 2014.
36. Meyer MS, Joshipura K, Giovannucci E, Michaud DS. A review of the relationship between tooth loss, periodontal disease, and cancer. *Cancer Cause Control* 2008; 19:895-907.
37. Hooper SJ, Wilson MJ, Crean SJ. Exploring the link between microorganisms and oral cancer: a systematic review of the literature. *Head Neck* 2009; 31:1228-39.
38. Homann N, Tillonen J, Meurman JH, Rintamäki H, Lindqvist C, Rautio M, Jousimies-Somer H, Salaspuro M. Increased salivary acetaldehyde levels in heavy drinkers and smokers: a microbiological approach to oral cavity cancer. *Carcinogenesis*. 2000; 21:663-8.
39. Väkeväinen S, Mentula S, Nuutinen H, Salmela KS, Jousimies-Somer H, Färkkilä M, Salaspuro M. Ethanol-derived microbial production of carcinogenic acetaldehyde in achlorhydric atrophic gastritis. *Scand J Gastroenterol* 2002; 37:648-55.
40. Salaspuro MP. Acetaldehyde, microbes, and cancer of the digestive tract. *Crit Rev Clin Lab Sci* 2003; 40:183-208.
41. Seitz HK, Cho CH. Contribution of alcohol and tobacco use in gastrointestinal cancer development. Cancer Epidemiology: Modifiable Factors. 2009:217-41.
42. Kurkivuori J, Salaspuro V, Kaihovaara P, Kari K, Rautemaa R, Grönroos L, Meurman JH, Salaspuro M. Acetaldehyde production from ethanol by oral streptococci.*Oral Oncol* 2007; 43:181-6.
43. Muto M, Hitomi Y, Ohtsu A, Shimada H, Kashiwase Y, Sasaki H, Yoshida S, Esumi H. Acetaldehyde production by non-pathogenic Neisseria in human oral microflora: Implications for carcinogenesis in upper aerodigestive tract. *Int J Cancer* 2000; 88:342-50.

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