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Review Article

Role of bacteria in oral carcinogenesis

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Abstract

Oral cancer is the most common cancer diagnosed in Indian men and is the leading cause of cancer deaths. It is considered as a multistep and multifactorial disease. Besides accumulation of genetic mutations, numerous other carcinogens are involved. In this category, viral and chemical carcinogens are well studied and documented. However, in the oral cavity, the role of microbiota in carcinogenesis is not known. Microbial populations on mouth mucosa differ between healthy and malignant sites, and certain oral bacterial species have been linked with malignancies, but the evidence is still weak in this respect. Nevertheless, oral microorganisms inevitably up-regulate cytokines and other inflammatory mediators that affect the complex metabolic pathways, and may thus be involved in carcinogenesis. Poor oral health associates statistically with prevalence of many types of cancer such as pancreatic and gastrointestinal cancer. This review presents possible carcinogenesis pathway involved in bacterial carcinogenesis, commonly implicated bacteria in oral carcinogenesis, and their role in cancer therapeutics as well.

Key words: Bacterial carcinogenesis, carcinogenesis, *Helicobacter pylori*, *Streptococcus anginosus*

Introduction

Head and neck carcinomas are biological heterogeneous group of cancers, in which oral cancer is the most common neoplasm. It is sixth common malignancy. Ninety percent of oral cancers are squamous cell carcinomas originating from the mucosal epithelium. They are the major cause of cancer morbidity and mortality worldwide, especially in the Indian subcontinent.[1,2]

The eminent British oncologist Willis has come closest and defined neoplasm as follows: "A neoplasm is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after cessation of the stimuli which evoked the change, even after the inciting stimulus is gone, it results from heritable genetic alterations that are passed down to the progeny of the tumor cells." These genetic changes allow excessive and unregulated proliferation that becomes autonomous (independent of physiologic growth stimuli), although tumors generally remain dependent on the host for their nutrition and blood supply. The entire population of cells within a tumor arises from a single cell that has undergone the genetic change, and hence tumors are said to be clonal.[3] It is a well-proven fact that these clonal changes in tumors occur in multiple steps and by multiple factors. As far as oral cancer is considered, 70–80% of oral cancer has been majorly linked to betel quid, tobacco chewing, smoking, and alcohol consumption. Other factors like genetic susceptibility of the individual, and external agents such as dietary factor may exert their synergistic role in tumorigenesis. [1]

The most common genetic alteration in oral cancer is mutation in tumor suppressor gene *TP53* and retinoblastoma gene (*Rb*). These mutations may be due to genetic alteration as in Li Fraumeni Syndrome or the effect of chemical carcinogenic agents and viral agents. Among the viral agents, association of human papilloma virus (HPV) is well documented. [1-3]

In the past decade, there has been increasing interest on the possible relationships between bacteria and the different stages of cancer development, but the association of bacteria with cancer of the oral cavity has yet to be adequately examined. So, in this review, we will discuss the relationship of bacteria and their role in different stages

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of cancer development by reviewing the English language literature available in Pub Med and other peer-reviewed journals.

Discussion

A large number of DNA and RNA viruses have proved to be oncogenic in a wide variety of animals, ranging from amphibia to primates, and the evidence grows stronger that certain forms of human cancer are of viral origin. The association between infection by the bacterium *Helicobacter pylori* and gastric tumors is well studied. It is thought that chronic infection with *H. pylori* leads to formation of lymphoid infiltrates in which B cells actively proliferate and may acquire genetic abnormalities, such as a t(11;18) translocation. Tumor growth is initially dependent on immune stimulation by *H. pylori*, but at later stages it no longer requires the presence of the bacterium.[3] Other bacteria which got widespread attention are *Salmonella typhi* in gall bladder cancer,[4-7] *Chlamydia trachomotis* with increased risk of cervical cancer,[1] and *Chlamydia pneumonia* and *Streptococcus bovis* linked with lung cancer and malignancies of colon subsequently.[8-15]

Possible pathway for bacterial carcinogenesis

In the vast majority of hepatocellular carcinomas, there is no consistent pattern of integration in the vicinity of known protooncogenes. It is therefore likely that the effect of HBV is indirect and possibly multifactorial. By causing chronic liver cell injury and accompanying regenerative hyperplasia, HBV expands the pool of cycling cells at risk for subsequent genetic changes. In the mitotically active liver cells, mutations may arise spontaneously or be inflicted by environmental agents such as dietary aflatoxins. Hepatitis C virus (HCV) is also strongly linked to the pathogenesis of hepatocellular carcinoma. As with HBV, the epidemiologic evidence of an association between hepatocellular carcinoma and HCV is compelling. The role of this virus in the pathogenesis of liver cancer seems to be related to its ability to cause chronic liver cell injury and inflammation that is accompanied by liver regeneration. Mitotically active hepatocytes, surrounded by an altered environment, are presumably prone to genetic instability and cancer development.[3] Like viral infection, bacterial infection also causes inflammation, regeneration of cells, and alteration in the surrounding stroma. In review of literature, compelling evidence for *H. pylori* has been documented for above mentioned tissue reaction.

There have been increasing data to confirm that bacterial infections rely upon precise interactions between the pathogens and components of the host cell regulatory systems, which are given below: [1]

1. It has been shown that several bacteria can cause chronic infections or produce toxins that disturb the cell cycle and lead to altered cell growth.[8,9,15]
2. Chronic infections induce cell proliferation and DNA replication through activation of mitogen activated kinase (MAPK) pathways and cyclin D1, and increase the incidence of cell transformation and the rate of tumor development through increased rate of genetic mutation.[16,17]
3. Several infections cause intracellular accumulation of the pathogen, leading to suppression of apoptosis primarily through modulation of the expression of Bcl-2 family proteins or by inactivation of retinoblastoma protein, pRb. [18,19] This strategy provides a niche in which the intracellular pathogen can survive in spite of the attempts of the host immune system to destroy the infected cells by apoptosis. Thus, it allows the partially transformed cells to evade the self-destructive process and progress to a higher level of transformation, ultimately becoming tumorigenic.[1]
4. Many pathogenic bacteria causing chronic infection with intracellular access subvert host cell signaling pathways, enhancing the survival of pathogen.[20] The regulation of these signaling factors is central to the development or inhibition of tumor formation. Such infections can mimic some of the gross effects seen intumorigenesis, and indeed the precancerous lesion formed in such infections can regress with antibiotic treatment and clearance of bacteria.[1]
5. Another possible mechanism is the metabolism of potentially carcinogenic substances by the bacteria. This is of relevance in the oral cavity, where the pre-existing local microflora may facilitate tumorigenesis by converting ethanol into its carcinogenic derivative, acetaldehyde, to levels capable of inducing DNA damage, mutagenesis, and secondary hyperproliferation of the epithelium.[21,22] Also, this is evident from the increased levels of microbial acetaldehyde production in heavy drinkers and smokers, supporting this concept.[23]
6. Microbial carcinogenesis may also involve nitrosation in which microbial cells catalyze the formation of *N*-nitroso compounds from the precursor's nitrite and amines, amides, or other nitrosatable compounds. Several species of bacteria encompass strains capable of catalyzing nitrosation, in particular, *Escherichia coli.* Also, yeasts and fungi may include nitrosating organisms. This particular nitrosamine appears to be a relevant candidate for causing carcinoma, not only of the esophagus but also of other mucosal areas such as the oral cavity.[24,25]
7. Recent studies have shown that podoplanin, a transmembrane glycoprotein, is expressed in various normal as well as neoplastic tissues. Butyric acid (BA), an extracellular metabolite from periodontopathic bacteria, plays an important role in the progression

of periodontal disease. BA/sodium butyrate (NaB) increases podoplanin expression and cell migration in certain oral squamous cell carcinoma (OSCC) cell lines, suggesting that the progression of periodontal disease may promote the progression of OSCC via a podoplanin-dependent pathway.[26]

Bacteria and oral cancer

It has been suggested that *H. pylori* infection might be associated with not only gastric ulcers but also gastric malignancies. Recently, it has been reported that the *Streptococcus anginosus* DNA sequence was found in DNA samples extracted from esophageal cancers. Because smoking and alcohol abuse are regarded as risk factors for both esophageal cancer and head and neck cancer, infection of *S. anginosus* might be associated with carcinogenesis of head and neck cancer.[27]

To investigate the involvement of *S. anginosus* infection in head and neck cancer, Tateda *et al* analyzed 217 DNA samples prepared from head and neck squamous cell carcinomas. By polymerase chain reaction (PCR) analysis, the *S. anginosus* DNA sequence was found in 217 out of 217 (100%) DNA samples obtained from head and neck cancers. By Southern blot analysis, positive bands were detected in 41 out of 125 (33%) samples. They could find no *S. anginosus* colony in oropharyngeal bacteriological culture dishes of 53 patients with and without head and neck cancer. On the other hand, they found the *S. anginosus* DNA fragment in eight out of eight DNA samples obtained from gingival smears by PCR analysis. These data indicate that the upper aerodigestive environment of the patients permitting *S. anginosus* infection is implicated in the carcinogenesis of head and neck squamous cell carcinoma.[27]

A hospital-based, case–control study was conducted on 20 patients with newly diagnosed oral cancer and 20 healthy controls without any cancer to evaluate the associations between *H. pylori* infection and oral cancer using culture and 16sRNA PCR technique for bacterial identification. However, the results of the pilot study suggest a possible association of *H. pylori* with an increased risk of oral cancer. Anand *et al* suggested additional studies in larger populations are necessary to confirm and quantify this possible association more accurately.[28]

Betel chewing has been shown to predispose to periodontal disease and oral cancer. Studies show that people with gum disease are more likely to test positive for *H. pylori*. It is not known if the lesions produced by betel quid and the resulting chemical changes predispose to colonization by *H. pylori*. Further, the role of this organism in oral cancer is not known. Author undertook a study to determine the presence of *H. pylori* in oral lesions of 30 oral cancer patients and to determine the presence of IgG antibodies to *H. pylori* in oral cancer patients who are betel chewers, non-betel chewers, healthy betel chewers, and healthy non-betel chewers, and to compare the presence of *H. pylori* in these four groups. One hundred and seventy-three subjects, of whom 53 were patients presenting with oral cancer to the Cancer Institute Maharagama, 60 were healthy betel chewers, and 60 were healthy non-betel chewers from the Religious and Welfare Service Centre Maharagama, were tested for *H. pylori* by serology. Thirty oral biopsies from oral cancer patients were cultured under microaerophilic condition to isolate *H. pylori*. Fourteen (26.4%) of the oral cancer patients tested positive for *H. pylori* by serology, of which two were also culture positive (only 30 samples were cultured). The presence of *H. pylori* in betel chewers (with or without cancer) compared to non-betel chewers was statistically significant (Chi-square test $P < 0.05$). The use of tobacco and areca nut in betel chewers was significant with the presence of *H. pylori* ($P < 0.05$). The oral cavity has been considered a potential reservoir for *H. pylori*, from where the organism causes recurrent gastric infections.[29]

In a case–control study, Rajendra *et al*. [30] concluded that the contribution of the *H. pylori* in dental plaque to mucosal inflammation and periodontal disease was significant. Logistic regression analysis showed gastrointestinal disease and poor oral hygiene as being the greatest risk factors for bacterial colonization, irrespective of the subject groups. A positive correlation exists between rapid urease test (RUT) reactivity and the frequency of mucosal inflammation. Further, they suggested the importance of sustained lymphocytic infiltration of the tissue reaction in oral submucous fibrosis, which is a premalignant condition.[31]

Mager *et al*.[32] investigated if the salivary counts of 40 common oral bacteria in subjects with an OSCC lesion would differ from those found in cancer-free (OSCC-free) controls. Unstimulated saliva samples were collected from 229 OSCC-free and 45 OSCC subjects and evaluated for their content of 40 common oral bacteria using checkerboard DNA–DNA hybridization. They concluded that high salivary counts of *Capnocytophaga gingivalis*, *Prevotella melaninogenica*, and *Streptococcus mitis* may be diagnostic indicators of OSCC.

Hooper *et al*. in 2006[33] conducted a study where, in order to characterize the bacterial microbiota present within oral cancerous lesions, tumorous and non-tumorous mucosal tissue specimens (approx. 1 cm^3) were harvested from ten OSCC patients at the time of surgery. A total of 70 distinct taxa were detected and 52 different phylotypes were isolated from the tumorous tissues and 37 taxa from within the non-tumorous specimens. Differences between

the composition of the microbiotas within the tumorous and non-tumorous mucosae were apparent, possibly indicating selective growth of bacteria within carcinoma tissue. Most taxa isolated from within the tumor tissue represented saccharolytic and aciduric species. Whether the presence of these bacteria within the mucosa has any bearing on the carcinogenic process is a concept worthy of further investigation.

In 2007, Hooper *et al*.[34] conducted a study with the primary objective to identify any bacterial species within OSCC tissue using a standard microbiological culture approach. At the time of surgery, a 1 cm^3 portion of tissue was harvested from deep within the tumor mass using a fresh blade for each cut. Diverse bacterial taxa were isolated and identified, including several putatively novel species. Most isolates were found to be saccharolytic and acid-tolerant species. Notably, some species were isolated only from either the tumorous or non-tumorous tissue type, indicating a degree of restriction. Successful surface decontamination of the specimens indicates that the bacteria detected were from within the tissue. Diverse bacterial groups have been isolated from within OSCC tissue. The significance of these bacteria within the tumor warrants further study.

Jukka [23] concluded in a review that microbial populations on mouth mucosa differ between healthy and malignant sites and certain oral bacterial species have been linked with malignancies, but the evidence is still weak in this respect. Nevertheless, oral microorganisms inevitably up-regulate cytokines and other inflammatory mediators that affect the complex metabolic pathways, and may thus be involved in carcinogenesis.

Sasaki *et al*.[35] assessed the frequency of *S. anginosus* infection in oral cancer tissues and investigated its infection route. The tissue specimens were obtained from 46 oral cancer and 3 precancerous leukoplakia subjects. *S. anginosus* DNA was frequently detected in squamous cell carcinoma (19/42), but not in other types of cancer (lymphoma and rhabdomyosarcoma) or leukoplakia samples. A subject-based analysis revealed that *S. anginosus* was solely detected in dental plaque and not in saliva from all 19 *S. anginosus*-positive squamous cell carcinoma cases. Further, the genotype of *S. anginosus* isolated from cancer tissue was identical to that from dental plaque of the same patients. They concluded that infection of *S. anginosus* could occur frequently in OSCC and that dental plaque could be a dominant reservoir of the *S. anginosus*.

Chocolatewala *et al*.[1] concluded in a review that studies have shown diversity of isolated bacterial taxa between the oral cancer tissue specimens and the control, with *Exiguobacterium oxidotolerans*, *P. melaninogenica*, *Staphylococcus aureus*, and *Veillonella parvula* being specific for tumorigenic tissues. Most isolates are saccharolytic and acid tolerant. *S. anginosus*, commonly linked with esophageal and pharyngeal cancers, is not of significance in oral cancers. Similarly, significant salivary specificity is noted for three bacteria, namely, *C. gingivalis*, *P. melaninogenica*, and *S. mitis*, in oral cancer patients, making these species salivary markers for the early detection of oral cancers, and thus improving the survival rate significantly.

Implication of bacteria in oral cancer therapeutics

The oral epithelium functions as a mechanical and protective barrier to resist bacterial infection. b-Defensins (BDs) are a group of antimicrobial peptides mainly produced by epithelial cells of many organs including skin, lung, kidney, pancreas, uterus, eye, and nasal and oral mucosa. This review focuses on BDs in oral epithelia and discusses their importance in oral epithelial health and disease. BDs exhibit antimicrobial activity against oral microbes including periodontitis-related bacteria, *Candida*, and papilloma virus. Alterative expression of BDs was observed in oral epithelial diseases, including oral inflammatory lesions with and without microbial infection and oral cancer. BDs may be useful in the treatment of oral infectious diseases, ulcerative lesions, and cancer. BDs play an important role in protection against oral microbes and may be used in clinical applications.[36]

Azurin, a cupredoxin type of electron transfer and purified low-molecular-weight redox protein from the pathogenic bacteria *Pseudomonas aeruginosa*, selectively induces and triggers apoptosis in certain human cancer cells.[37] Recently, Yamada *et al*.[38] reported that azurin can effectively enter human cancer cells but not normal cells. After internalization, azurin forms a complex with the tumor suppressor protein p53 and stabilizes it,[39] thereby inducing apoptosis or cell cycle arrest in the G1 phase.[40,41] Despite extensive analysis of azurin's antitumor activity, its ability to modulate oral cancer growth has not yet been characterized. In this study, the antitumor effect of azurin on YD-9 and MG-63 cells is elucidated. Azurin controls p53 and cyclin B1 protein levels, leading to apoptosis of OSCC. Furthermore, combination treatment of azurin with 5-fluorouracil or etoposide effectively increases the sensitivity of OSCC to anticancer drugs.[37]

Increasing epidemiological evidence supports the view that dietary flavonoids have protective roles in oral diseases, including cancer. However, the dietary forms of flavonoids, the flavonoid glycosides, must first be hydrolyzed to the aglycones, which is thought to occur mainly in the intestine. Author tested whether this hydrolytic activity occurs in the oral cavity. Their evidence supported the

contention that salivary hydrolysis of certain flavonoid glucosides may be important in some individuals but not in others. Support for a bacterial contribution to this hydrolysis was obtained from the inhibitory effect of antibacterials *in vivo* and *in vitro* and from experiments with subcultured oral bacterial colonies. However, cytosol isolated from oral epithelial cells was also capable of effective hydrolysis. Dietary flavonoid glucosides may thus be hydrolyzed in the oral cavity by both bacteria and epithelial cells that are shed, to deliver the biologically active aglycones at the surface of the epithelial cells. The aglycones quercetin and genistein both potently inhibited proliferation of oral cancer cells. The large interindividual variability in this hydrolytic activity may be a factor that should be taken into consideration in future studies.[42]

Comprehensive comparison of the salivary microbiota between patients with pancreatic cancer and healthy control subjects revealed a significant variation of salivary microflora. The authors observed associations between variations of patients' salivary microbiota with pancreatic cancer and chronic pancreatitis. This report also provides proof of salivary microbiota as an informative source for discovering non-invasive biomarkers of systemic diseases.[43]

Conclusion

Studies on bacterial carcinogenesis are lacking; unlike HPV, direct link of bacteria to oral cancer cannot be proved by available literature. Yet, there is a significant difference in oral bacteria in cancerous and non-cancerous tissues. We can hypothesize that like HBV and HCV, bacteria can maintain inflammation in surrounding stroma by induction of certain inflammatory cytokines, which have a role in carcinogenesis and invasion. Furthermore, research in the the role of bacteria in induction of tumor-induced macrophage which has immunosu prresive effect on the tumor, will throw more light in to bacterial carcinogenesis Prognosis of bacterial induced oral cancer may be good because this can be easily counteracted by antimicrobials and induction of certain beneficial biological reactions in cancer tissue, as mentioned in treatment aspect of the present review.

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