Review Article

Role of bacteria in oral carcinogenesis

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Abstract

Oral cancer appears to be increasing in incidence, and mortality has hardly improved over the past 25 years. Better understanding of the etiopathogenesis should lead to more accurate and earlier diagnosis and more effective treatments with fewer adverse effects. Despite increasing interest in the possible relationships between bacteria and the different stages of cancer development, the association of bacteria with cancer of the oral cavity has yet to be adequately examined. Different bacteria have been proposed to induce carcinogenesis, either through induction of chronic inflammation or by interference, either directly or indirectly, with eukaryotic cell cycle and signaling pathways or by metabolism of potentially carcinogenic substances like acetaldehyde, causing mutagenesis. This review presents the possible carcinogenesis pathway involved in bacterial carcinogenesis, commonly implicated bacteria in oral carcinogenesis and their role in cancer therapeutics as well.

Key words: Bacteria, carcinogen, oral cancer

INTRODUCTION

Oral cancers rank sixth among the common malignancies globally, with a rising titer of around 40% in developing countries such as southeast Asia. Among these, 90% of all oral cancers are squamous cell carcinoma (SCC) originating from the mucosal epithelium.[1]

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[2] Although scientific knowledge in viral oncology has exploded in the 20th century, the role of bacteria as mediators of oncogenesis is less well elucidated. As cancer continues its climb as the leading cause of death in developed nations, understanding the long-term effects of bacteria has become increasingly important as a possible means of cancer prevention. A transmissible cause of cancer was suspected as early as the 16th century. However, it was not until the late 20th century that reproducible, peer-reviewed work definitively identified a bacterial cause of malignancy.[3]

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Interest in the possible relationships between bacteria and the different stages of cancer development has been increased since the classification by the World Health Organization of *Helicobacter pylori* as a definite (class 1) carcinogen. The three main examples are infection with the bacterium *Helicobacter pylori* leading to an elevated risk of developing pancreatic cancer, gastric adenocarcinoma and gastric lymphoma, infection with particular types of human papilloma virus (HPV) leading to cervical cancer, tonsillar carcinoma and some cases of oral squamous cell carcinoma (OSCC) and chronic hepatitis B and C infections leading to hepatocellular carcinoma.[4]

HISTORY

Ever since 1890, when the pathologist William Russell described "a characteristic organism of cancer," there has been a small but dedicated group of scientists who have claimed that bacteria (not viruses) cause cancer. Their reports showed an unusual microbe that can be seen microscopically in cancer tissue and cultured from cancerous tumors and blood. Similar bacteria have been reported in certain noncancerous diseases as well. The idea that bacteria cause major forms of cancer was discarded a hundred years ago by the medical

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establishment—and is still regarded as scientific heresy. Bacteria derived from cancer are generally considered as "laboratory contaminants" or "secondary invaders" or "opportunistic infections" of weakened cancerous tissue. Nevertheless, this communication provides evidence that "cancer microbes" can be demonstrated microscopically in cancer tissue.[5]

Livingston was the physician in 1974 who found that cancer bacteria could produce the fetal growth hormone hCG. Adding to this discovery were the findings of other independent researchers who discovered that cancer cells are also capable of producing or synthesizing hCG.

Cancer bacteria display intracellular parasitism during certain life-cycle phases and can invade healthy cells. They can also secrete toxic chemical fractions such as actinomycin-D, which may result in karyotypic changes, resulting in malignancy.

After the onset of cancer, bacteria act in concert with cancer cells and, in a way that is not fully understood, help cancer cells synthesize hCG.

- hCG is a universal cancer marker that also acts as a protective hormone for the cancer cell. Paradoxically, hCG protects the growing fetus from host immunity.[6]

DISCUSSION

There is increasing evidence that some pathogenic bacteria can contribute to specific stages in cancer development, particularly in chronic infections where, for the duration of the infection, normal cell processes can come under the influence of factors released by the pathogen.[7] An overwhelming body of evidence has determined that relationships among certain bacteria and cancers exist. Research has found that certain bacteria are associated with human cancers. Their role, however, is still unclear. Convincing evidence links some species to carcinogenesis while others appear promising in the diagnosis, prevention or treatment of cancers. The complex relationship between bacteria and humans is demonstrated by *Helicobacter pylori* and *Salmonella typhi* infections. Research has shown that *Helicobacter pylori* can cause gastric cancer or MALT lymphoma in some individuals. In contrast, exposure to *Helicobacter pylori* appears to reduce the risk of esophageal cancer in others. *Salmonella typhi* infection has been associated with the development of gallbladder cancer; however, *Salmonella typhi* is a promising carrier of therapeutic agents for melanoma and colon and bladder cancers. Thus, bacterial species and their roles in particular cancers appear to differ among different individuals. Many species, however, share an important characteristic: Highly site-specific colonization. This critical factor may lead to the development of noninvasive diagnostic tests, innovative treatments and cancer vaccines.[8]

Bacteria and carcinogenesis

It has been reported that the majority of cases of head and neck cancer can be related to tobacco use and heavy alcohol consumption. Other possible risk factors include viral infections, poor oral hygiene and infection with Candida species. The latter microorganisms are associated with some forms of leukoplakic lesions, the presence of which has long been recognized as an independent risk factor for carcinoma. The involvement of other microorganisms, particularly bacteria, has not been studied to any great extent.[9] Cancer has been referred to as a molecular disease of cell membrane glycoconjugates. Certain glycoconjugates serve as receptors for specific bacteria, and recent reports support the notion that shifts in the colonization of different cancer cells are associated with observed changes in cell surface receptors. It is now recognized that bacteria bind to and colonize the mucosal surfaces in a highly selective manner via a "lock and key" mechanism. Adhesins on bacteria bind specifically to complementary receptors on the mucosal surfaces of the host. These adhesins differ from species to species, leading to specificity in attachment to different surfaces.

Studies have shown that even within genera, colonization patterns of individual species may differ markedly; *Streptococcus salivarius*, for example, preferentially colonized the oral soft tissues and saliva compared with the teeth, while the reverse was true of *Streptococcus sanguis.*[10]

Bacterial infections have been linked to malignancies due to their ability to induce chronic inflammation.[11] There have been increasing data to confirm that bacterial infections rely upon precise interactions between the pathogens and the components of the host cell regulatory systems that are given below.

- 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[1,12,13]
- Chronic infections induce cell proliferation and DNA replication through activation of mitogen-activated kinase pathways and cyclin D1 and increase the incidence of cell transformation rate of tumor development through increased rate of genetic mutation[1,14,15]
- 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.[16,17] 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 tumorogenic
- Many pathogenic bacteria causing chronic infection with intracellular access subvert host cell signaling pathways, enhancing the survival of the pathogen.[18]

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 in tumorogenesis, and indeed the precancerous lesion formed in such infections can regress with antibiotic treatment and clearance of bacteria.

- Another possible mechanism is the metabolism of potentially carcinogenic substances by the bacteria. This is of relevance in the oral cavity, where the preexisting local microflora may facilitate tumourogenesis by converting ethanol into its carcinogenic derivative, acetaldehyde, to levels capable of inducing DNA damage, mutagenesis and secondary hyperproliferation of the epithelium.[19,20]

Also, this is evidential from the increased levels of microbial acetaldehyde production in heavy drinkers and smokers, supporting this concept.

- 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*[21] Also, yeasts and fungi may include nitrosating organisms. This particular nitrosamine appears to be a relevant candidate for the cause of carcinoma, not only of the esophagus but also of other mucosal areas such as the oral cavity[22]
- 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[1]
- Certain bacterial infections may evade the immune system or stimulate immune responses that contribute to carcinogenic changes through the stimulatory and mutagenic effects of cytokines released by inflammatory cells
- These include reactive oxygen species (ROS), interleukin-8 (IL-8), cyclooxygenase-2 (COX-2), reactive oxygen species (ROS) and nitric oxide (NO).

Chronic stimulation of these substances along with environmental factors such as smoking or a susceptible host appears to contribute significantly to carcinogenesis.[8]

The microbial flora associated with oral carcinomas

There is indeed a delicate balance between the microbial flora and our immune system, which allows the microbial flora to live as a commensal organism with us. But, when disease occurs, these microbial flora become aggressive, giving rise to a host of diseases, some of which are inflammatory, while others are degenerative, cancerous or transitory.[23]

Studies reveal that, relative to the contiguous healthy oral mucosa, the human oral carcinoma surface biofilms harbored significantly increased levels of both aerobes and anaerobes.[24] Many cancer centers have reported an increase in quinolone-resistant bacteria (primarily *Escherichia coli* and *Pseudomonas aeruginosa*) in patients receiving quinolone prophylaxis.[25] High levels of colonization of OSCC by facultative oral Streptococci were observed in the saliva of OSCC subjects (Sasaki *et al.*, 1998; Sakamoto *et al.*, 1999; Tateda *et al.*, 2000; Shiga *et al.*, 2001). More recently, viable bacteria have been isolated from both superficial and deep portions of the OSCC (Hooper *et al.*, 2006; Hooper *et al.*, 2007), revealing that the tumor microenvironment is well suited for bacterial survival.

The role of bacteria in the development of oral cancer has not been delineated, but the persistent presence of bacteria at tumor sites in the oral cavity raises intriguing questions about the role of bacteria in the progression of OSCC. Unfortunately, most of such studies to date have included only cultured oral bacterial species, using classical cloning and sequencing approaches (Nagy *et al.*, 1998; Mager *et al.*, 2005; Hong *et al.*, 2006). To establish the association of oral bacteria in the progression of OSCC, the complete bacterial profile (cultured and uncultured) in the oral cavity of OSCC subjects needs to be first determined.[26]

According to a study by Nagy *et al.*, no large differences were observed for the biofilm flora at

the tumor and control sites when the distributions of aerobic species were investigated. Almost similar species were found with the same frequency at both sites (both tumor and normal sites), with the exceptions of *Serratia liquefaciens, Klebsiella pneumoniae* and *Citrobacter freundii* from the Gram negative species and *Streptococcus J-haemolyticus* and *Enterococcus faecalis* from the Gram positive bacteria, which were present more frequently at the tumor sites. Anaerobic bacteria with known pathogenic features, such as Actinomyces, Clostridium, Fusobacterium, Prevotella, Porphyromonas and members of the *Bacteroides ureolyticuslgracilis* group, were involved in the biofilm formation on the tumor surface, while they were found only occasionally on the healthy mucosa surface of the same patient. Veillonella, a known member of the normal oral flora, was also isolated from twice as many lesion sites as control sites (18 versus nine). In one patient, the microaerophyl Capnocytophaga was present on the tumor surface.[24]

Mager *et al.* (2005) reported that several species detected in the nontumoros control tissue were not detected in the tumor tissues, and vice versa. For instance, *Exiguobacterium oxidotolerans*, *Prevotella melaninogenica*, *Staphylococcus aureus*, *Veillonella parvula* and species of Bacteria and Micrococcus were isolated only from tumoros specimens and not at all from nontumoros ones. Conversely, *Moraxella osloensis*, *Prevotella veroralis* and species of Actinomyces were grown only from nontumoros tissues. This could indicate that while bacteria are present within all the oral mucosal tissues, there are potentially significant differences between the microfloras within tumoros compared with nontumoros mucosae.[10]

In many studies, it was noticed that smoking and alcohol consumption were commonly associated with carcinoma of the palate, while that of chewing tobacco was commonly associated with carcinoma of the alveolus and buccal mucosa. It has been stated that alcohol is not carcinogenic, but there is increasing evidence that a major part of the tumor-promoting action of alcohol might be mediated via its first, toxic and carcinogenic metabolite, acetaldehyde. Acetaldehyde is produced from ethanol in the epithelia by mucosal alcohol dehydrogenases, but much higher levels are derived from microbial oxidation of ethanol by the oral microbial flora. Thus, subjects consuming alcohol are at increased risk of developing cancer because of this synergistic action. Gram positive bacteria and yeasts are associated with higher acetaldehyde production, which could be a biologic explanation for the observed synergistic carcinogenic action of alcohol and smoking on upper gastrointestinal tract cancer. This may open a new microbiologic approach to the pathogenesis of the cancer of the oral cavity and upper gastrointestinal tract. *Streptococcus intermedius*, Prevotella, Capnocytophaga and *Candida albicans* were isolated in increased numbers at carcinoma sites.

Sasaki *et al.* (2005) assessed the frequency of *Streptococcus anginosus* infection in oral cancer tissues and investigated its infection route. The tissue specimens were obtained from 46 oral cancers and three precancerous leukoplakia subjects. *Streptococcus 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 *Streptococcus anginosus* was solely detected in dental plaque and not in saliva from all 19 *Streptococcus anginosus*-positive squamous cell carcinoma cases. Further, the genotype of *Streptococcus anginosus* isolated from cancer tissue was identical to that from dental plaque of the same patients. They concluded that infection of *Streptococcus anginosus* could occur frequently in OSCC and that dental plaque could be a dominant reservoir of the *Streptococcus anginosus* bacteria.[27]

According to a study by Mager *et al*. (2005), Devlin PM investigated whether 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.[10]

In a review, Mager *et al.* (2006) concluded that certain bacterial infections may evade the immune system or stimulate immune responses that contribute to carcinogenic changes through the stimulatory and mutagenic effects of cytokines released by inflammatory cells. Bacterial toxins can kill cells or, at reduced levels, alter cellular processes that control proliferation, apoptosis and differentiation. These alterations are associated with carcinogenesis and may either stimulate cellular aberrations or inhibit normal cell controls.[8]

In 2006, Hooper *et al.* conducted a study with the primary objective to identify any bacterial species within the 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 tumoros or the nontumoros 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 the OSCC tissue. The significance of these bacteria within the tumor warrants further study.[10]

Hooper *et al.* in 2007 conducted a study where, in order to characterize the bacterial microbiota present within the oral cancerous lesions, tumoros and nontumoros mucosal tissue specimens (approximately 1 cm^3) were harvested from 10 OSCC patients at the time of surgery. Bacteria were visualized within sections of the OSCC by performing fluorescent *in situ* hybridization with the universal oligonucleotide probe, EUB338. DNA was extracted from each aseptically macerated tissue specimen using a commercial kit. This was then used as a template for polymerase chain reaction (PCR) with three sets of primers, targeting the 16S rRNA genes of Spirochaetes, Bacteroidetes and the domain bacteria. Differences between the composition of the microbiotas within the tumoros and nontumoros mucosae were apparent, possibly indicating selective growth of bacteria within the 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.[28]

In a case–control study, Rajendra *et al*. (2009) evaluated the role of *Helicobacter pylori* in the etiology of mucosal inflammation, a condition that compounds the morbid state associated with oral submucous fibrosis. A rapid urease test (RUT) of plaque samples was performed to estimate the *Helicobacter pylori* bacterial load. They concluded that the contribution of *Helicobacter 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 RUT reactivity and the frequency of mucosal inflammation.[29]

In 2009, Fernando and Jayakumar *et al.* undertook a study to determine the presence of *Helicobacter pylori* in the oral lesions of 30 oral cancer patients and to determine the presence of IgG antibodies to *Helicobacter pylori* in oral cancer patients who are betel chewers, nonbetel chewers, healthy betel chewers and healthy nonbetel chewers, and to compare the presence of *Helicobacter 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 nonbetel chewers from the Religious and Welfare Service Centre Maharagama, were tested for *Helicobacter pylori* by serology. Thirty oral biopsies from oral cancer patients were cultured under microaerophilic conditions to isolate *Helicobacter pylori*.

Of the −53 oral cancer patients, −44 were betel chewers. Among the 53 oral cancer patients examined, 10 of −44 (22.7%) patients who are betel chewers and four of nine (44.4%) patients who are nonbetel chewers were detected to be positive for IgG antibody against *Helicobacter pylori*. In the healthy group (betel chewers and nonbetel chewers), 10/60 (16.7%) of the healthy betel chewers tested positive for *Helicobacter pylori* by serology. None of the healthy nonbetel chewers tested positive for *Helicobacter pylori*.

Fourteen (26.4%) of the oral cancer patients tested positive for *Helicobacter pylori* by serology, of whom two were also culture positive (only 30 samples were cultured). The presence of *Helicobacter pylori* in betel chewers (with or without cancer) compared with nonbetel 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 *Helicobacter pylori* ($P < 0.05$). The oral cavity has been considered a potential reservoir for *Helicobacter pylori*, from where the organism causes recurrent gastric infections. They conclude from their study that there is a significantly higher proportion of *Helicobacter pylori* in betel chewers compared with nonbetel chewers but not between oral cancer patients compared with patients without oral cancer. Hence, betel chewing may predispose to colonization with *Helicobacter pylori* in the digestive tract through swallowing the quid or during betel chewing.[30]

Jukka in 2010 concluded in a review that microbial populations on the oral 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.[31]

Chocolatewala *et al*. in 2010 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*, *Pseudomonas melaninogenica*, *Staphylococcus aureus* and *Veillonella parvula* being specific for tumorigenic tissues. Most isolates are saccharolytic and acid tolerant. *Streptococcus 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 *Candida gingivalis*, *Pseudomonas melaninogenica* and *Streptococcous mitis*, in oral cancer patients, making these species salivary markers for the early detection of oral cancers and thus improving the survival rate significantly.[1]

Pushalkar *et al.* in 2011 concluded that the most prevalent genera in the OSCC library were Streptococcus, Gemella, Rothia, Peptostreptococcus, Porphyromonas and Lactobacillus. To understand the role of bacteria in the development of oral cancer, the first step is to identify both cultured and uncultured organisms in the saliva as these organisms have the potential to cause inflammation that may support OSCC progression.[26]

Anand *et al.* in 2011 conducted a hospital-based, case–control study on 20 patients with newly diagnosed oral cancer and 20 healthy controls without any cancer to evaluate the associations between *Helicobacter pylori* infection and oral cancer using culture and 16sRNA PCR technique for bacterial identification. *Helicobacter pylori* was identified by culture in one control (1/20) and three cases (3/20). The presence of *Helicobacter pylori* was confirmed by PCR of the cultured organism and various biochemical tests. However, the results of the pilot study support the association of *Helicobacter pylori* with oral cancers, although the odds ratio is not statistically significant and the strength of the association suggests a possible association with high-risk behavior in oral cancer cases. Furthermore, it was found that *Helicobacter pylori* DNA was not unique to cancerous oral tissue as PCR from controls was also positive for two of 20 controls. Although a cause-and-effect relationship cannot be inferred from this study, our findings can serve as a pilot study for further studies of *Helicobacter pylori.*[32]

Metgud *et al.* (2014) assessed the microbial flora using cultured saliva and oral swabs from subjects with OSCC and healthy controls. The culture plates were incubated at 37˚C for 48 h, after which the bacterial growth was analyzed. They concluded from their study that the median number of colony forming units (CFUs)/mL at the carcinoma site were significantly greater than that at the contralateral healthy mucosa. Similarly, in the saliva of carcinoma subjects, the median number of CFUs/mL were significantly greater than in the saliva of healthy controls.[33]

Bolz *et al.* (2014) conducted a clinical study to identify the bacterial spectra on the surface of OSCC in comparison with the oral mucosa of patients with a higher risk to emerge an OSCC and control group to determine their susceptibility to various common antibiotics. They concluded from their study that the prominent pathogens of the normal healthy oral mucosa were aerobes. The ratio between aerobes and anaerobes was 2:1, balanced in risk patients and inverted in the OSCC group.[34]

CONCLUSION

There is increasing evidence that some pathogenic bacteria can contribute to specific stages of cancer development. In particular, chronic infections triggered by bacteria can facilitate tumor initiation or progression because, during the course of infection, normal cell functions can undergo the control of factors released by the pathogen. These bacterial factors, namely virulence factors, can directly manipulate the host regulatory pathways and the inflammatory reaction. The challenge of finding and understanding the true associations between bacterial infections and human cancers is indeed great. Many of the bacterial infections that promote oncogenesis, by disrupting the oral mucosal surface, allow bacterial invasion and perhaps serve as a point of entry to the regional lymph nodes. This indicates that although the bacterial biota were commensals of the oral cavity, they may become pathogenic when their balance is disturbed. Unlike viral infections, bacterial infections are typically curable, and the prospect of antibiotic treatments to prevent, alleviate or cure cancers is obviously alluring. Vaccination against etiologic pathogens to prevent infection and thus eliminate the risk of cancer is yet another hopeful prospect for researchers.

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