

Bacteria in oral carcinogenesis

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Abstract

Cancer is a subject that has got enormous depth and we clinicians are still searching for the end point. The multi centric etiopathogenesis of cancer makes it a field of enormous research. Bacteria meanwhile have been seen to cause or acts as an aggravating stimuli in different cancers of the body including the oro-facial region. Bacteria induce carcinogenesis via chronic inflammation, directly or indirectly via interference, may be by metabolism of potentially carcinogenic substances like acetaldehyde causing mutagenesis. The routes are many but still needs lot of research. This review article deals with the basic knowledge of carcinogenesis caused by bacteria in oro-facial region.

Keywords: Multi centric, Interference, Acetaldehyde, Mutagenesis, Research.

Introduction

WHO defines cancer as; “a generic term for a large group of diseases characterized by the growth of abnormal cells beyond their usual boundaries that can then invade adjoining parts of the body and/or spread to other organs.”

Being a multi centric condition cancers have various etiological factors. That vast area includes genetic mutations, virus, cigarettes, alcohol and various other chemical carcinogens. A transmissible cause of cancer was suspected as early as 16th century. However it was not until the late 20th century that reproducible, peer-reviewed work definitively identified a bacterial cause of malignancy.¹

Oral cancers ranks 6th among the common malignancies around the world.² it has a rising titre of around 40% in south east Asia.³ Among these 90% are squamous cell carcinoma.⁴

Most of the cases of oral cancers have been related to chronic tobacco use, chronic betel quid chewing and especially in the indian subcontinent different forms of gutkha have been a major etiological factor. Cases due to viral infections especially HPV (human papilloma virus) and EBV (Epstein barr virus) are also present. The carcinogenic action of viruses through abrogation of tumor suppressor genes like p53 and pRb and alteration of host genomes have been well documented with enough evidence.⁵

With extensive studies and research now a days the role of bacteria has been found as well in the carcinogenesis of oro facial cancers.

History and Evidence

1890 was the year when pathologist William Russel described bacteria as “characteristic organism of cancer”; since then there has been scientists with school of thought that bacteria not viruses are the predominant microbes causing cancer.⁶

Moreover Livingston in 1974 found that cancer causing bacteria can synthesize fetal hormone hCG(human chorionic gonadotropin) and as hCG is an universal cancer marker which even acts as protective hormone for cancer cells the role of bacteria has become enormously important in carcinogenesis.⁷

There has been many cases where bacterial specific cancers have been reported; the most common of them are Helicobacter pylori which causes gastric ulcers that can lead to gastric carcinomas, Chlamydia trachomatis can cause cervical carcinomas, Salmonella typhi infections can lead to gall bladder cancers, Chlamydia pneumoniae infections can lead to lung cancer, Mycobacterium bovis related endocarditis can lead to intestinal cancer.

Mechanisms of Carcinogenesis by Bacteria

There are different mechanisms through which bacteria can lead to carcinogenesis. The different procedures have been described via a flowchart. (Fig. 1).

The different mechanisms have been explained as:

Bacteria in different ways can cause chronic infections along with production of toxic substances which may lead to certain changes in the host like distortion of cell cycle which can further lead to altered cell growth.⁸

Chronic infections induce cell proliferation and DNA replication through activation of mitogen activated kinase (MAPK) pathways and cyclin D1. This increases the incidence of cell transformation rate of tumour development through increased rate of genetic mutation.⁸

The infections causes intracellular accumulation of pathogen which can lead to suppression of apoptosis primarily through modulation of expression of bcl-2 protein or by inactivation of pRb; retinoblastoma protein. This mechanism gives the bacteria the ability to

stay in the host unharmed as the apoptotic factors of the hosts are inactivated and thus the cancer caused by bacteria also evade the host immune responses via this mechanism only.⁹

Bacteria especially those residing in the oral cavity have an ability to transform ethanol into acetaldehyde; which is carcinogenic. High levels of acetaldehyde in heavy drinkers and smokers validate this theory. Through high levels of acetaldehyde bacteria can cause DNA damage, mutagenesis and secondary hypoproliferation of epithelium mainly in oral cavity.¹⁰

Other mechanism is via nitrosation where the bacteria forms N-nitroso compounds from precursors like nitrites, amides, amines and other nitrosatable compounds. Among bacteria mainly *E. coli* species and certain yeast and fungi are capable of this process. These nitrogen compounds exerts carcinogenic effects in esophagus and oral mucosa.¹¹

Certain recent studies have shown a compound called podoplanin, which is a transmembrane glycoprotein which is expressed in both normal and neoplastic tissue lines. Butyric acid and sodium butyrate is an important metabolite for bacteria causing periodontal disease and these metabolites increases podoplanin expression and cell migration in certain oral squamous cell carcinoma cell lines. This theory suggests that progression of periodontal disease may promote oral squamous cell carcinoma via a podoplanin dependent pathway.⁸

Certain bacteria even evade the immune system of host and cause immune responses that can induce carcinogenic changes via formation of interleukin-8 (IL-8), reactive oxygen species (ROS), cyclooxygenase-2 (COX-2) and nitric oxide (NO).¹²

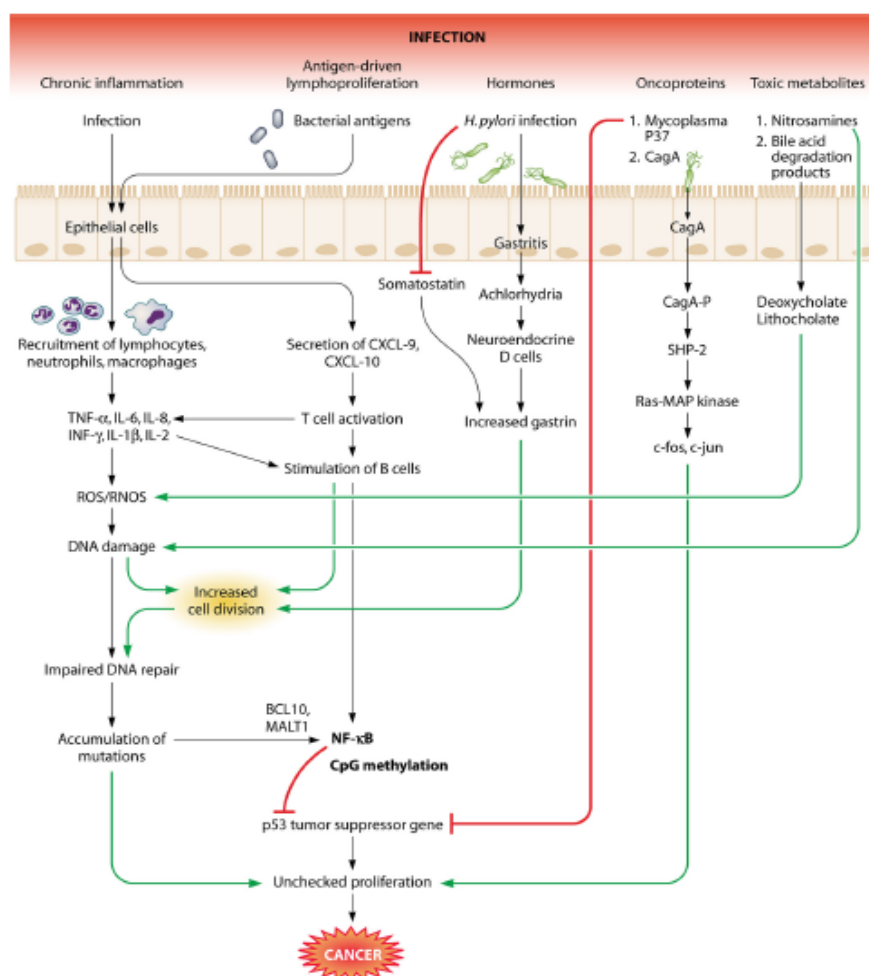


Fig. 1: Mechanisms of oncogenesis caused by bacteria

Bacteria in Oral Cancer

Interests in relationship of bacteria with different stages of development of cancer increased with the announcement of *Helicobacter pylori* as class I carcinogen by WHO.¹³

High levels of facultative Streptococci in the saliva of patients with oral squamous cell carcinoma has been reported through various studies done by Sasaki et al. (1998), Sakamoto et al. (1999), Tateda et al. (2000) and Shiga et al. (2001).¹³

Hooper et al. (2006, 2007) have done different studies in oral squamous cell carcinoma patients to find the bacteria that are residing in such tissues. In 2006 he found out that mainly saccharolytic and aciduric bacteria were present in oral squamous cell carcinoma tissues. In 2007 he identified diverse microbes from the deep portion of oral squamous cell carcinoma tissues.^{14,15}

Fernando and Jayakumar et al. (2009) in his study found that people who are betel chewers have more chances of having *H.pylori* in their oral cavity than the non-betel chewers. *H.pylori* is one of the commonest sources of gastric ulcers and gastric carcinoma.¹⁶

Similarly Rajendran et al. (2009) in a case control study concluded that *H.pylori* has significant contributions in dental plaque, mucosal inflammation and periodontal diseases. Rapid urease test (RUT) was performed via samples taken from dental plaque of some patients and it was found that there was a positive co-relation between RUT reactivity and mucosal inflammation. Mucosal inflammation has also been commonly associated with oral submucous fibrosis which is a potentially malignant condition.¹⁷

Mager et al.(2005) in a study of 229 oral squamous cell carcinoma free patients and 45 oral squamous cell carcinoma patients found out that the saliva of oral squamous cell carcinoma patients had high salivary count of certain bacterial species which was different from those patients who were cancer free. The bacterial species found were *Capnocytophaga gingivalis*, *Prevotella melaninogenica*, *Streptococcusmitis*. He concluded that these bacterial species may act as indicators for oral squamous cell carcinoma.¹⁸

Sasaki et al. (2005) in his study obtained tissue specimens from 46 oral cancer patients and 3 leukoplakia patients. The oral cancer patients were having squamous cell carcinoma, rhabdomyosarcoma and lymphoma. He found that *Streptococcus angiosus* DNA was frequently isolated from patients with oral squamous cell carcinoma but not from lymphoma, rhabdomyosarcoma and leukoplakia. It was mainly found in dental plaque and not saliva thus concluding that patients with oral squamous cell carcinoma get frequently infected by *Streptococcus angiosus*.¹⁹

Nagy et al. (1998) in his study found that as far as aerobic species of bacteria were concerned not much difference was seen between the species from tumor and normal sites. Some exceptions from gram negative family like *Serratia liquefaciens*, *Klebsiella pneumoniae*, *Citrobacter freundii* and certain gram positive species like *Streptococcus J haemolyticus* and *Enterococcus faecalis* were found more in tumor sites. Anaerobic species like *Actinomyces*, *Fusobacterium*, *Clostridium*, *Prevotella*, *Porphyromonas* and members of *Bacteroides ureolyticus/gracilis* group were predominantly found in tumor/cancerous sites.²⁰

Chocolatawala et al. (2010) in a review study concluded that certain bacterial species like

Exiguobacterium oxidotolerans, *Pseudomonas melaninogenica*, *Staphylococcus aureus*, *Veillonella parvula* are specific for tumor/cancerous sites. The study also concluded that 3 bacterial species namely *Pseudomonas melaninogenica*, *Streptococcus mitis* and *Candida gingivalis* were isolated from saliva of oral cancer patients making them useful salivary markers for early detection of oral cancers. This early detection can lead to early treatment plans and preparations that can lead to better survival rates in such patients.⁸

Pushalkar et al. (2011) concluded in his study that most prevalent bacterial species found in oral squamous cell carcinoma patients were *Streptococcus*, *Gemella*, *Rothia*, *Peptostreptococcus*, *Porphyromonas* and *Lactobacillus*.²¹

Metgud et al. (2014) in his study concluded that number of colony forming units (CFU/ml) of bacteria was significantly higher in oral cancer sites than from the normal health mucosa.²²

Discussion

Oral cancer ranks among the top three cancers in the Indian subcontinent and is a major threat to the population of this region. Oral cancer is defined as cancer of lips, mouth and tongue which is adopted and confirms to definition of oral cavity cancers by International Classification of Diseases (ICD) coding scheme, WHO case definition and also for International Agency for Research and Cancer.²³ Multiple causes and risk factors have been attributed to oral cancer over the years. All these factors have been studied and well explained.

Microbial aspect of oral cancers for a major portion of time was mainly attributed to viruses like Human Herpes Virus-8 (HHV-8), Human Papilloma Virus (HPV) and Epstein Barr Virus (EBV). In recent times multiple studies have tried to explain the bacterial connection via various theories and studies and some of them have proved promising results. Announcement of *Helicobacter pylori* as class I carcinogen by WHO and association of *Streptococcus* genera with oral squamous cell carcinoma by the studies of Sasaki et al.(1998), Sakamoto et al.(1999), Tateda et al. (2000) and Shiga et al. (2001) have proved fruitful.¹³

The different studies mentioned in this article point towards a probable relationship between oral and bacteria and needs to be studied extensively to provide with better theories. This relationship can even give us a new perspective of diagnosis and treatment planning in oral cancer cases.

Conclusion

More and more studies have shown and predicted that certain bacterial species are somehow related to different stages of oral cancers, probable theories of carcinogenesis of bacteria has also been laid down. However bacterial carcinogenesis in oral cancer is a road that has not been travelled much. We clinicians

can hypothesize that the bacteria species through chronic infections, inflammations, mutagenesis and formation of inflammatory mediators like IL and ROS can cause or act as an aggravating factors in certain oral cancers. More efforts and deeper studies are needed to clearly prove these theories. The positive result can only help clinicians around the globe in better treatment planning and increase the survival rates of oral cancer patients.

Conflict of Interest: The authors state that this article does not engender any conflicts of interest whatsoever with any organization or individual.

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