Review

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Role of Oral Microbiota in Carcinogenesis: A Short Review

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A strong and healthy microbiome is responsible for homeostasis between the host and microbiota which is necessary to achieve the normal functioning of the body. Dysbiosis provokes prevalence of pathogenic microbes, leading to alterations in gene expression profiles and metabolic processes. This in turn results in anomalous immune responses of the host. Dysbiosis may be associated with a wide variety of diseases like irritable bowel syndrome, coeliac disease, allergic conditions, bronchitis, asthma, heart diseases and oncogenesis. Presently, the links between oral microbial consortia and their functions, not only in the preservation of homeostasis but also pathogenesis of several malignancies have gained much awareness from the scientific community. The primary intent of this review is to highlight the dynamic role of oral microbiome in oncogenesis and its progression through various mechanisms. A literature search was conducted using multiple databases comprising of PubMed, Scopus, Google Scholar, and Cochrane electronic databases with keywords including microbiome, microbiota, carcinogenesis, tumorigenesis, and immunosuppression. Current and the past literature has pointed out the role of microorganisms in oncogenesis. It may be put forth that both the commensal and pathogenic strains of oral microbiome play an undeniably conspicuous role in carcinogenesis at different body sites.

Key Words Carcinogenesis, Immunosuppression therapy, Microbiota, Mouth

INTRODUCTION

The development of human beings after birth is characteristically viewed as an exclusive system of organ evolution. But perhaps we are missing a part of the picture. Humans are not mere individuals but a complex biological system harboring trillions of microbial cells [1,2]. Human body serves as a habitat for a wide array of microorganisms, which in conglomeration with their genetic matter constitute a comminity, referred to as the microbiome [2]. Human microbiome that may be depicted as an “essential organ” bears almost 100-fold more microbial genes than does the host genes [3-5]. Each organ or site of the body harbors a diverse population of pathogens that are dynamically milled alongside human development from birth through adolescence [4].

Human microbiome is known to colonize different sites such as skin, oral mucosa, respiratory tract, gastrointestinal (GI) tract, urogenital tract and so on [6]. Additionally, it is worthy to note that the composition of the microbiome and their function vary according to different sites, gender, ethnicity, and nutrition status of the host [7]. It is now widely accepted that these microbes are not just passive passengers but play a crucial role in normal growth, resistance to disease, and immune response. For instance, microbiota aid in vitamin biosynthesis protects against pathogens, influences innate immune responses, modulates the metabolic phenotype and regulates epithelial development [7]. Thus, the microflora helps in maintaining the homeostasis, thereby making normal functioning of the body achievable [6,7].

Just as microbiota is important in healthy functioning of the human body, it has a definitive role in dysfunction and disorders too [4]. Any disturbance in the homeostasis may result in dysbiosis, allowing some pathogens to become more prevalent and eventually leading to the diseases. Dysbiosis can alter host gene activity and metabolic processes, which in turn results in an anomalous immune response of the host [8]. Dysbiosis can contribute to the onset of a disease in several different ways. These include “gain of function dysbiosis”,

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wherein the functions of the pathogens can be acquired or their disproportionate growth may promote disease; “suppression or loss of functioning” of the normal commensals; “combination of both”. In other words, dysbiosis may be characterized by the loss of commensal organisms, unwarranted growth of potentially injurious organisms, and loss of general microbial miscellany [8].

Currently, the evidence is expanding rapidly that a disruption in the normal development or maintenance of the microbiome is causally related to a broad array of ailments including irritable bowel syndrome, coeliac disease, allergic conditions, bronchitis, asthma, heart disease, atherosclerosis, obesity, diabetes, autism, Alzheimer’s disease, etc. [9]. Besides aforementioned disorders, cancer, a devastating global health problem, is not an exemption in which microbiota is involved [9]. Human microbiome research is steadily gaining impetus for proposition of alternative mechanisms underlying cancer development and progression [10,11]. Cancer has been described as one of the principal causes of death globally, with more than 17 million cases detected in 2018 [12]. It is projected that 15% to 20% of cancers are caused as a result of infectious entities [13-16]. Thus, the microbiome is receiving a great deal of attention in recent years given its influence on cancer.

In the pathogenesis of cancer, the microbiome plays a dual role. The brighter side is their contribution to plummeting the onset of cancer by escalating the host immune system. The dark side involves their involvement in carcinogenesis and reduction in the efficacy of anti-tumor agents [2,17]. Furthermore, it is controversial whether cancer is the result of variation in the microbiota, or whether modifications in the normal microbiome are the result of cancer growth. Tumor cells exhibit different profiles of microbiome compared to untransformed progenitors. Moreover, the hypoxic environment and nutrient availability in solid tumors can favor organisms that require low oxygen tension. On the other hand, there is growing evidence that disruption of microbial communities colonizing specific organs is directly or indirectly associated with carcinogenesis [18].

The majority of our observations regarding the role of microbiome in development of human cancer are based on the studies of GI tract, since it harbors 99% of the microbial mass contributing to the gross metabolic function of the body [3]. There are fewer studies on oral microbiome and its role in carcinogenesis. Understanding how oral microbiomes impact cancer develpoment and progression at different body sites could bring new opportunities for cancer prevention, treatment, and management [17]. The current review was set with an aim to scrutinize different lines of data regarding the function of the oral microbiota as a threat to different body sites in cancer development. In addition, the fundamental role of oral microbiota in oncogenesis is discussed.

ORAL MICROBIOME

As compared to the other sites in human body, the oral cavity constitutes a unique and challenging environment for microbial growth and survival, since it undergoes high fluctuations in nutrient supply, pH, temperature, sheer and mechanical forces from mastication and oral hygiene practices, as well as exposure to various chemicals, encluding pharmaceuticals and toxicants [19]. Yet the oral cavity encompasses a wide array of rich and diverse ecosystem comprising hundreds of microbes like bacteria, fungi and viruses, living in a specific and organized manner in different sites of the oral cavity [20-22]. These begin as the flora passed on to the newborn from the mother; following eruption of both the primary and permanent dentitions; and with change in both supra- and sub-gingival niches (i.e. dental plaque/biofilm) [23].

In the normal physiological conditions, there exists a vibrant synergistic interaction among healthy oral microbial populations; however in the disease state, there is a shift towards a narrower diversity of healthy populations with predominance of the pathologic populations in combination with an erratic inflammatory host immune response [23]. Currently, the oral microbiome has attracted considerable attention as it appears to be a strong marker of dental health and a contributor to an amplified peril of systemic disorders including GI diseases like pancreatitis, ulceritive colitis, and cirrhosis of liver. In addition, many other disorders like Alzheimer’s disease, obesity, diabetes, polycystic ovarian disease, rheumatoid arthritis and cardiovascular diseases have been linked to oral microbiome [22,24]. Further, oral microbiota has an undeniable role in cancer development [25].

Bacteria

Much of the scientific research is focused on the salival bacterial microbiota since they are predominant as compared to the other oral biomes (viral, fungi, archaea, and protozoa biomes) [19]. Approximately 700 bacterial species have been identified in the oral cavity, making it the second largest bacterial reservoir in the human body, after the GI tract. The most common bacterial species in the oral cavity belongs to the *Gemella*, *Granulicatella*, *Streptococcus*, and *Veillonella* genera [26].

Numerous theories have been suggested to enlighten the potential role of oral bacteria in carcinogenesis, but the underlying biological mechanisms remain unclear [27]. The following describes the putative mechanisms of carcinogenesis that are regulated by commensal microorganisms:

1. Chronic inflammation: Environmental exposure or infection may elicit inflammation which might play a significant role in cancer induction, progression, invasion and metastasis [10]. Activation of the inflammatory cells by microorganisms may result in production of nitric oxides, hydrogen peroxide, reactive lipids, etc. which are responsible for production of cytokines. Cytokines involved in dysregulated cell growth

include TNF-α, interleukin (IL)-1, IL-6, IL-8, granulocyte-macrophage colony-stimulating factor and VEGF [28-30]. The most frequently found oral commensal bacteria responsible for aggravating an inflammatory response and infections are *Porphyromonas gingivalis* (*P*. *gingivalis*) and *Fusobacterium nucleatum* (*F*. *nucleatum*) [31].

2. Cellular proliferation: The microbial endotoxins may trigger disruption of the cell cycle, altered cell growth, and mutations in tumor suppressor genes and proto-oncogenes [32].

3. Cellular apoptosis: Microbes like *P*. *gingivalis* and *F*. *nucleatum* cause activation of anti-apoptotic signaling pathways, thereby resulting in cancer growth and survival while inhibiting pro-apoptotic pathway [32].

4. Cellular invasion: Bacteria especially *P*. *gingivalis* is known to activate certain pathways that produce enzymes like cysteine proteinases and matrix metallopeptidase 9. This promotes passage of oncocytes into blood vessels and lymphatics by dilapidation of the basement membrane and extracellular matrix which eventually allows for extension and metastases at distant sites [33].

5. Production of carcinogenic substances: Some bacteria are involved in the production of certain substances that possess a strong carcinogenic potential. Lipopolysaccharide that is produced by many anaerobic oral microbes like *Streptococcus oralis*, *Streptococcus mitis*, *Streptococcus sanguinis*, *Lactobacillus fermentum*, *Lactobacillus acidophilus*, *Bifidobacterium adolescentis*, etc. has the ability to stimulate inflammatory processes implicated in carcinogenesis [34]. Furthermore, hydrogen sulfide and reactive oxygen species produced by *Fusobacterium* and *Porphyromonas* are linked to colorectal neoplasia. *Bacteroides* and *Firmicutes* species ferment excessive host protein into sulfides and nitrosamines, triggering DNA alkylation and mutations. Glycosulfatase in *Bacteroides* catalyzes the conversion of sulfomucins to sulfides, contributing to mucin degradation and carcinogenesis. Acetaldehyde derived from *Neisseria* and *Streptococcus* can cause DNA damage. Additionally, interaction of bacteria and their metabolites with toll-like receptors (TLRs) of the innate immune system was found to promote carcinogenesis in the colon, pancreas, liver, and skin [30].

Bacterial species that have been known to play a role in oncogenesis are *F*. *nucleatum* and *P*. *gingivalis*. *F*. *nucleatum* is an anaerobic, gram negative, bacterium predominantly present in the oral cavity and the gut. The bacterium harbors an array of membrane and surface proteins responsible for invasion of multiple cell types including epithelial cells of oral cavity and colon and may also instigate tumorigenesis. It has been reported that *F*. *nucleatum* plays a role in oral cancer, coloreactal cancer, and esophageal cancer [35]. *P*. *gingivalis* is an anerobic, gram negative bacterium actively involved in the pathogenesis of periodontal destruction. It has the ability to invade nearby tissue and hasten the process of tumorigenesis. It has also been reported that the bacterium moves to the other parts of oro-digestive tract. It also plays a role in pathogenesis of pancreatic cancer [35].

Viruses

Human oral viral biome is a highly conserved and personalized community; to such a degree that its composition can vary depending on the host's sex. Bacteriophages constitute the majority of oral viral biome and exhibit a very stable lytic/lysogenic cycle. The lytic cycle can completely change the oral bacterial community by either exterminating the bacterial species or imparting new functions on the oral bacterial community [36]. Some of these bacteriophages are associated with *Veillonella* and *Streptococcus* spp. that constitute the main commensal bacterial genera in the oral cavity [37]. In healthy patients, the main bacteriophage families found in the oral cavity are *Siphoviridae*, *Myoviridae*, and *Podoviridae*; all belonging to the *Caudovirus* order [38]. Thus, it could be suggested that the oral viral microbes play a crucial role in controlling and regulating the oral bacterial community.

So far, *Herpesviridae*, *Papillomaviridae*, and *Anelloviridae* are among the most common eukaryotic virus families present in healthy patients. Among them, human papillomavirus (HPV), human cytomegalovirus, herpes simplex virus type-1, and Epstein–Barr virus, have been found in asymptomatic healthy individuals [19]. However, only few studies have evaluated the oral viral community, and more studies are necessary to evaluate the precise role of the viruses in the oral microbiome.

Viruses are responsible for 10% to 15% of human cancers globally. Their role in tumorigenesis may be allied to genomic instability, mutations, aberrations, and DNA damage. Viruses tend to cause cancer by inducing chronic inflammation and immunosuppression or through direct actions of their own oncogenic proteins [39]. Chronic inflammation may endorse carcinogenesis through discharge/release of nitric oxide, cytokines and chemokines, which in turn arbitrates DNA damage, cell proliferation and angiogenesis [40].

Human immunodeficiency virus (HIV) can localize in the oral cavity via gingival crevicular fluid, and HIV inflicted subjects carry a significantly elevated threat to develop certain types of cancer, such as Kaposi sarcoma, cervical cancer, Hodgkin's or Non-Hodgkin's lymphoma, anal cancer, pulmonary cancer and testicular cancer [41,42]. Oral mucosa is the initial site for HIV-Kaposi sarcoma in approximately 20% of patients [41]. HPV is responsible for the etiology of papilloma, condylomas, focal epithelial hyperplasia, head and neck squamous cell carcinoma, etc. [41]. Epstein–Barr virus is known to release virions in the saliva by replication in the nasopharyngeal and salivary gland epithelial cells and lysing them. It can be infected predominantly in the oral cavity or head and neck region as seen in Burkitt's lymphoma, mononucleosis, or oral hairy leukoplakia, and the prevalence and disease severity are increased in individuals co-infected with HIV [42].

Table 1. Association between oral microbiome and cancers of different body parts

Type of cancer	Oral pathogens
Oral cancer	*Porphyromonas gingivalis* (*P. gingivalis*), *Capnocytophaga*, *Dialister*, *Filifactor*, *Catonella*, *Peptostreptococcus*, *Human papillomavirus* (*HPV*)
Lung cancer	*Prevotella*, *Veillonella*, *Capnocytophaga*
Pancreatic cancer	*P. gingivalis*, *Aggregatibacter*, *Neisseria*, *Leptotrichia*
Esophageal cancer	*P. gingivalis*, *Fusobacterium nucleatum* (*F. nucleatum*), *Bacteroidales*, *Lautropia*, *Tannerella forsythia* (*T. forsythia*), *Treponema denticola*
Gastric cancer	*Prevotella*, *Veillonella*
Hepatic cancer	*Oribacterium*
Colorectal cancer	*F. nucleatum*, *Parvimonas*, *Peptostreptococcus*
Cervical cancer	*HPV*
Breast cancer	*P. gingivalis*, *T. forsythia*, *Fusobacterium*, *Prevotella*

Fungi

Among the identified oral fungal species, three (*Aspergillus*, *Fusarium* and *Cryptococcus*) are known to be pathogenic in humans and are not known to be oral colonizers, though it is proposed that the pathogenicity of these fungal species might be controlled by other commensal oral fungi [43]. In addition, *Malassezia* genera has been described as a skin commensal and an opportunistic pathogen associated with scalp disorders and is being considered a predominant member of the commensal 'basal oral mycobiome' [44].

The most common commensal fungi and members of the basal oral mycobiome belong to *Candida* genera, which are found in 70% of healthy patients [19]. *Candida albicans* is regarded as the most common opportunistic pathogen, causing infection in immunocompromised situations due to the great compliance to different host niches. It is detected in the oral cavity, esophagus, respiratory tract, GI tract, liver, vagina, penis and skin [45]. *Candida* infection has a strong propensity to induce dysplastic changes in the oral epithelium by production of endogenous nitrosamines, acetaldehydes, and overexpression of some oncogenic molecules [46].

Acetaldehyde has been categorized as a group I human carcinogen by the International Agency for the Research on Cancer. It is produced in the body by oral microflora and from ethanol in the epithelium by mucosal alcohol dehydrogenases. Alcohol dehydrogenase is produced by a wide array of species including *Streptococcus mitis*, *S. oralis*, *S. salivarius*, *S. sanguinis* and *Candida.* Alcohol dehydrogenase metabolizes alcohol to acetaldehyde which in turn exerts mutagenic effects via a variety of processes including DNA cross-linking, adduction, aneuploidy, or chromosomal aberrations [47]. It has been reported that *Candida* infection is associated with malignancies of oral cavity, lip, thyroid gland, skin, and blood [48].

Table 1 shows the commensals found in the oral cavity that are frequently related (directly or indirectly) to a variety of cancers in distant organs [31,33,47,49,50].

CONCLUSION

Oral cavity is regarded as the chief microbial stockroom in human body, and the microbial variations might be vastly linked to oncogenesis. Oral microbiome (both commensal and pathogenic) plays an incontestably conspicuous role in carcinogenesis. Illuminating the role of oral microbiome in etiology and pathogenesis of cancer will open new ways for the development of novel markers for early detection (or markers of susceptibility) and new strategies for targeted therapeutic applications in the future. However, to emphasize their clinical translation into an effective prognostic/diagnostic biomarker, meticulous research and comprehensive corroboration of high-throughput technologies and large-scale clinical trials will be indispensable. This could prove to be extremely promising and path-breaking to achieve our goal of conquering cancer.

CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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