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IMPORTANCE OF DETERMINATION OF ORAL MICROBIAL PROFILE IN ORAL CANCER PATIENTS-NEW CONCEPT IN CANCER DEVELOPMENT

Microbiology

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ABSTRACT

Oral squamous cell carcinoma (OSCC) is an invasive epithelial neoplasm that is influenced by various risk factors, with a low survival rate and an increasing death rate. In the past few years, with the verification of the close relationship between different types of cancers and the microbiome, research has focused on the residential changes of oral bacteria and their role in OSCC. Generally, oral bacteria participates in OSCC development by influencing normal apoptosis, facilitating invasion and metastasis, promoting cell proliferation and angiogenesis, and assisting cancer stem cells. Antimicrobial resistance is emerging among cancer patients. Advancement and monitoring of the microbiota will improve our understanding of the role of the microbiota in carcinogenesis and open new perceptions for future therapeutic and prophylactic modalities.
Our review aims to summarize these findings and raise our perspectives. We conclude that different oral bacteria show distinct alterations in the abundance and a certain combination of various bacteria might possibly be markers for OSCC diagnosis. Therefore, oral bacteria may be a target to provide potential methods for early diagnosis and more effective treatments.

KEYWORDS

oral squamous cell carcinoma; microbiome

INTRODUCTION-

Oral cancer (predominantly squamous cell carcinoma) is a part of head and neck cancers (HNCs) affecting the oral cavity proper, i.e.,mouth anterior to the palatine tonsils, also referred to as intraoral. In the International databases, oral cancer is classified as “lip and oral cavity”: ICD-10 sites C00-C06. These constitute the 16th most prevalent malignancy worldwide, accounting for an estimated 247,563 new cases and 177,384 deaths annually [1]. There is, however, marked geographical and cultural variation. In much of South Asia, for example, oral cancer is the most common cancer among males, perhaps sixth among women, and second overall [2]. In the USA, the corresponding numbers are ~35,130 and 7410, respectively, although the anatomical sub-sites do not precisely match those used in the worldwide data.

There is a male predilection and the tongue is the most commonly affected sub-site [3]. In the West, nearly 74% of oral squamous cell carcinoma (OSCC) cases are attributed to tobacco smoking and heavy alcohol consumption [4], while in South Asia and the Pacific, smokeless tobacco and areca (betel) nut chewing are the major risk factors [5]. Unlike cancers of the oropharynx, only a small fraction of OSCC cases (2–6%) are attributed to human papilloma virus (HPV) infection [6, 7]—although greater proportions are reported from the Asia-Pacific Region—but there are questions about definitions of head and neck sub-sites and laboratory methods [8]. Around 20% of all OSCC cases remain unexplained by any of the known risk factors. In addition, and despite advances in cancer treatment modalities, OSCC continues to have poor prognosis with 5-year survival rates less than 50% in much of the world [9, 10]. These challenges have triggered scientists to search for novel risk factors and prognosis modifiers that eventually could present targets for preventive or therapeutic interventions. Particularly, there has been increasing interest in the role of the oral microbiome in oral carcinogenesis [11].

Oral Microbiome-

The oral cavity harbours the second most diverse microbial community in human body, being second only to the gut (12).The oral microbiome is composed of different communities, predominated by bacteria, followed by fungi and viruses inhabiting the human oral cavity both in suspended (or planktonic) phase in saliva as 'salivary microbiome' and attached to biotic and abiotic surfaces as the 'biofilm microbiome'. The resident bacteria in the biofilm interact both synergistically and antagonistically. Metabolic forces of bacteria inhabiting the biofilm operate synergistically to break down complex host macro molecules such as mucin to obtain nutrients. Subsequently, cascades of food chains manifest in the biofilm where the metabolic product of one organism becomes a primary nutrient for another. Furthermore, bacterial cells communicate by signaling with each other, using a range of diffusible molecules which facilitate the coordination of gene expression among members of the microbial community. Peptides are used for communication between Gram positive bacteria. The microbial diversity varies between different surfaces of the mouth depending on the prevailing physical and biological conditions. Nevertheless, biofilms with higher microbial diversity are found on the highly papillated surfaces of the tongue. Teeth are nonshedding surfaces and the highest amount of biomass in the mouth can be seen on them.

The maximum numbers and greatest diversity of oral microbiota are found at stagnant sites which provide protection from oral removal forces . Fissures on occlusal surfaces equipped with high numbers of aerobic and facultatively anaerobic, saccharolytic Gram positive bacteria predominantly streptococci. Moreover, there are few anaerobes or Gram negative bacteria. However, the highest proportion of proteolytic and many Gram negative obligate anaerobes are present in the gingival crevice.

Oral microflora and oral cancer risk link

In a study of oral carcinomas, Nagy *et al*. revealed that the surface of tumors showed increased numbers of certain members of the oral microbiota as compared to the control sites.[13] Rajeev *et al*. (2012) analyzed 217 DNA samples prepared from the head-and-neck squamous cell carcinomas to examine the involvement of *Streptococcus anginosus* infection in the head-and-neck cancer.[14] Sasaki *et al*. concluded that infection of *S. anginosus* could occur frequently in OSCC and that dental plaque could be a dominant reservoir of the *S. anginosus*.[15] Mager *et al*. determined the relationship of 40 common salivary bacteria counts between oral cancer patients and controls and reported that OSCC patients tend to have significantly elevated concentrations of certain bacteria in their saliva. High salivary counts of *Capnocytophaga gingivalis, Prevotella melaninogenica* and *Streptococcus mitis* could serve as potential diagnostic indicators of OSCC.[16] Another similar study also found raised concentrations of bacteria in the saliva of oral cancer patients. In 2006, Hooper *et al*. conducted a study where in he found the difference between bacterial microbiota composition present within the tumorous and non-tumorous mucosa were apparent, perhaps indicating selective growth of bacteria within carcinoma tissue.[18]

Commensal bacteria are the species of bacteria that live in equilibrium with the host immune defenses ,While the link of pathogenic bacteria and oral cancer cannot be denied. *Streptococcus* is most often the predominant genus in the healthy oral microbiome, and less frequently *Prevotella, Veillonella, Neisseria* and *Actinomyces, Fusobacterium, Porphromonas, Treponema*, Eubacteria, Lactobacterium, *Capnocytophaga, Eikenella, Leptotrichia, Peptostreptococcus, Propionibacterium* and *Haemophilus* dominate an individual's oral microbiome.[19] Commensal bacteria compete for nutrients and

receptors with exogenous microorganisms rendering them a critical component of the innate host defense system. They also produce antagonists such as bacteriocins that cause inhibition of susceptible extrinsic bacteria. In addition, lipopolysaccharide of the microbiota, maintain a persistent expression of MHC class II molecules on macrophages and other cells and stimulate the cross-protective antibody production. In other words, the resident microflora serves as a barrier to the exogenous species thus contributing to the host defense mechanism.

Inter-relationship of oral microflora, alcohol and oral carcino genesis

The literature review also suggests that Neisseria, a frequent inhabitant of the oral mucosa, possess high alcohol dehydrogenase enzymatic activity that converts ethanol to acetaldehyde which is an established carcinogen. The ability of the oral microflora to produce acetaldehyde in ethanol incubation was also investigated by Srinivasprasad *et al.* (2015).[17]

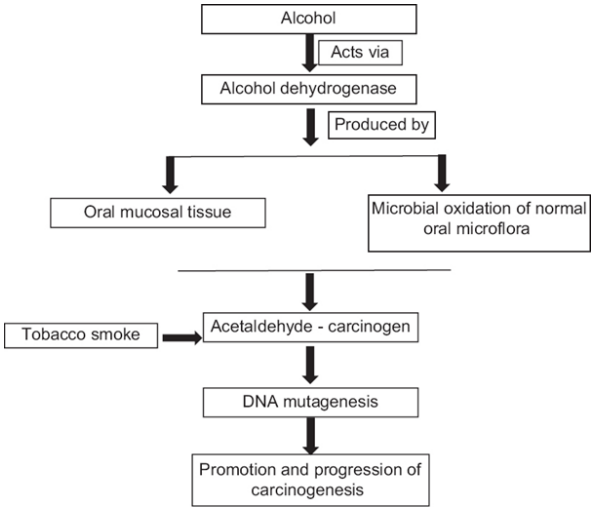

Figure 1: Interrelationship of oral microflora, alcohol and oral carcinogenesis

Numerous studies confirm this hypothesis ,that the local microflora may promote carcinogenesis by converting ethanol into its first and genotoxic metabolite acetaldehyde, and till date, streptococci, or other Gram-positive aerobic bacteria, and yeasts have been linked with acetaldehyde production. Acetaldehyde is not only produced from ethanol in the epithelia by mucosal alcohol dehydrogenases but also much higher levels are obtained from microbial oxidation of ethanol by the oral microflora.[22] Acetaldehyde has been classified as a group I carcinogen to humans by the International Agency for the Research on Cancer and is supported by several epidemiological and biochemical studies.[23].

Homann *et al.* showed that smokers even after moderate alcohol intake revealed up to seven times higher concentrations of salivary acetaldehyde compared with nonsmokers.[21] Tobacco smoke contains acetaldehyde and repeated exposure to it might lead to the selection of microbes that are capable of high rate acetaldehyde metabolism and are more tolerant to acetaldehyde. According to Salaspuro and Salaspuro, Homann *et al*.[20],[21] chronic smoking modifies oral flora to produce more acetaldehyde from ethanol. This indicates that the saliva of oral cancer patients has increased potential for harboring more microbial flora. Thus, the oral bacterial flora may act in synergy with the primary risk factors such as alcohol abuse and smoking in the oral cancer pathogenesis. Since, the oral microbiome is one of the most important sources of local acetaldehyde, improving oral hygiene can interfere with this acetaldehyde production [Figure 1].

CONCLUSION-

There is growing epidemiological evidence regarding the link between oral microflora and malignancies. Both pathogenic and the commensal strains of bacteria seem to play a role in oral carcinogenesis. To conclude, it can be safely postulated that though the normal oral bacterial flora may not have a direct role in epithelial dysplasia and OSCC, possibilities of their involvement exist when they occur in conjunction with other known etiological factors such as smoking and alcohol consumption. Since the ecologic shift from the resident microflora to the nonresident pathogenic microbes is a significant finding in oral carcinogenesis, maintenance of oral hygiene in these patients is warranted.

Furthermore, clinicians need to be aware of the beneficial protective properties of the resident microflora, and their treatment strategies should be focused on the control rather than the elimination of these organisms. The normal microbial composition of the body is believed to have major health benefits for the host which brings up the incorporation of the concept of stabilizing microbiota that is compatible with health as a means to maintain oral health. “Prebiotics” (agents that encourage the growth of the normal microflora) and “probiotics” (the deliberate use of organisms to restore colonization resistance) may become available. Avoiding alcohol and tobacco would be the best way to reduce local aldehyde exposure to the oral mucosa. A thorough exploration of the biological behavior of the altered oral microbiota by isolating the various strains associated with oral cancer and profiling them using next-generation sequencing methods may be productive in the assessment of their exact role if at all in carcinogenesis and their usefulness in the therapeutic regime of OSCC. Fluctuations in the oral commensal microflora in association with cancer development can serve as a potential diagnostic indicator.

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