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RESEARCH ARTICLE

CORRELATION IN BETWEEN ORAL BACTERIAL FLORA AND ORAL CANCER- A REVIEW ARTICLE.

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Abstract

The oral cavity has the second largest and diverse microbiota after the gut harboring over 700 species of bacteria. Many works have also shown that the oral periopathogens Fusobacterium nucleatum and Porphyromonas gingivalis play an important role in the development of colorectal and pancreatic cancer. Oral microflora may serve as a synergistic factor with the other commonly known risk factors such as alcohol abuse and smoking. In the present article, we hypothesize a causal role for oral bacterial flora in oral cancer although an indirect one. We propose that the normal bacterial flora in conjunction with the already established risk factors such as alcohol consumption may play a role in cancer development.

Introduction:-

The term "microbiome" is coined by Joshua Lederberg, a Nobel Prize laureate, to describe the ecological community of symbiotic, commensal and pathogenic microorganisms. Oral microbiome was first identified by the Dutchman Antony van Leeuwenhoek who first identified oral microbiome using a microscope constructed by him. The community of microbial residents in our body is called the microbiome.[1] Oral cavity is inhabited by a diverse microflora that may include bacteria, fungi, mycoplasma, protozoa and possibly viral flora of which bacteria are the predominant group.[2]

Heterogeneous nature of the oral tissues and structures provide a diverse and unique ecological habitat to the oral Microorganisms. Microorganisms that are distributed in various niches such as dorsum of the tongue, mucosal surfaces, teeth and saliva. Bacterial flora plays an active role in the maintenance of the oral health.[3]

S.mitis are detected in most or all oral sites, whereas several species were quite site specific. For example, Actinomyces spp., S. sanguinis, S. gordonii, and Abiotrophia defectiva appeared to preferentially colonize the teeth. S. salivarius was found mostly on the tongue dorsum. S. intermedius preferentially colonized the subgingival plaque in most of the subjects but was not detected in most other sites.[4]

Organisms Associated With Various Periodontal Diseases [5]

Periodontal disease	Microorganisms
Gingivitis	Streptococcus sanguis Streptococcus milleri Actinomyces israelii Actinomyces naeslundii

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	Prevotella intermedia Capnocytophaga spp. Fusobacterium nucleatum Veillonella spp.
Pregnancy gingivitis	Prevotella intermedia
Adult periodontitis	Porphyromonas gingivalis Prevotella intermedia Fusobacterium nucleatum Tannerella forsythia Treponema denticola Aggregatibacter Actinomycetemcomitans
Aggressive periodontitis — Localized chronic	Aggregatibacter Actinomycetemcomitans Porphyromonas gingivalis Prevotella intermedia Capnocytophaga spp. Eikenella corrodens Neisseria spp. Aggregatibacter Actinomycetemcomitans
Prepubertal periodontitis	Fusobacterium spp. Selenomonas spp. Campylobacter spp. Prevotella spp. Capnocytophaga spp.
Refractory periodontitis	Tannerella forsythus Porphyromonas gingivalis Campylobacter rectus Prevotella intermedia
Acute necrotizing ulcerative periodontitis (ANUG)	Prevotella intermedia Treponema spp.

Most Common Bacteria Isolated In Dentoalveolar Abscess[6]

Facultative anaerobes	Obligate anaerobes
Streptococcus milleri	Peptostreptococcus species
Streptococcus sanguis	Porphyromonas gingivalis
Actinomyces spp.	Prevotella intermedia
Fusobacterium nucleatum	

Specific Oral Bacterial Species Have Been Implicated In Several Systemic Diseases, Such As-[4]

1. Bacterial endocarditis
2. Aspiration pneumonia
3. Preterm low birth weight
4. Cardiovascular disease

Microbial composition have been implicated in several diseases such as diabetes, dental caries and periodontal diseases.[3]

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. 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.[3]

According to Vogtmann & Goedert (2016), tooth loss and periodontitis are associated with increased esophageal cancer risk pointing to a possible role of the oral microbiome in malignancy.[8]

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. High salivary counts of Capnocytophaga gingivalis, Prevotella melaninogenica and Streptococcus mitis could serve as potential diagnostic indicators of OSCC. Infection of S. anginosus could occur frequently in oral squamous cell carcinoma and that dental plaque could be a dominant reservoir of the S. Anginosus.[9]

Papilloma viruses are found in many oral cancers and are also capable of transforming cells to a malignant phenotype.[10]

In 2006, Hooper et al. conducted a study wherein 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. Streptococcus is most often the predominant genus in the healthy oral microbiome. 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.[3]

Inter-Relationship Of Oral Microflora, Alcohol And Oral Carcinogenesis

Bacterial infections have been linked to malignancies due to their ability to induce chronic inflammation.[11]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. 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.[12]

High alcohol dehydrogenase enzymatic activity that converts ethanol to acetaldehyde which is an established carcinogen. Microflora may promote carcinogenesis by converting ethanol into its first and genotoxic metabolite acetaldehyde.Streptococci, Gram-positive aerobic bacteria, and yeasts have been linked with acetaldehyde production. 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.[3]

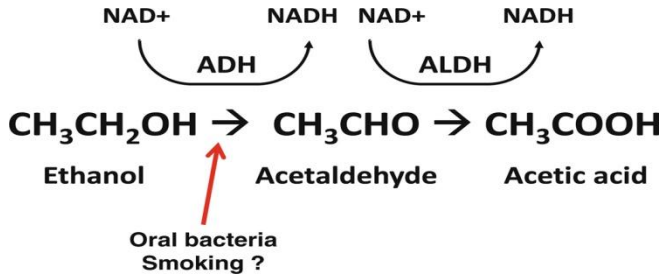

Figure 1:-Oral bacteria in alcohol metabolism. Under normal physiological conditions, ethanol is metabolized to acetaldehyde by alcohol dehydrogenase (ADH), and acetaldehyde is further metabolized to acetic acid by aldehyde dehydrogenase (ALDH). Oral bacteria have the capacity to convert ethanol to acetaldehyde, a genotoxin, leading to extended acetaldehyde exposure of the oral and gastrointestinal tract, following alcohol use, and possibly potentiated by smoking.[13]

Acetaldehyde produces mutagenic effects such as DNA adducts, DNA cross-linking, aneuploidy, or chromosomal aberrations by inducing DNA damage. According to Salaspuro, Homann et al chronic smoking modifies oral flora to produce more acetaldehyde from ethanol.[14]

The oral microbiome is one of the most important sources of local acetaldehyde, improving oral hygiene can interfere with this acetaldehyde production.[3] 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.[14]

Inter-Relationship Of Oral Microflora, Oral Hygiene And Oral Carcinogenesis

Oral microorganisms inevitably up-regulate cytokines and other inflammatory mediators that affect the complex metabolic pathways, and may thus be involved in carcinogenesis.[15] Periodontal disease involves a shift in bacterial flora in the gums, accompanied by a potentially pathogenic inflammatory response. Kang et al., (2009) revealed a significant increase in the levels of Porphyromonas gingivalis and Candida albicans in cancer group than in normal controls. Streptococcus anginosus in dental plaque could cause infection of the oral mucosa which may lead to DNA damage due to the increased synthesis of NO and cyclooxygenase-2 resulting in carcinogenesis of the infected tissues. OSCC surfaces show significantly raised levels of Porphyromonas and Fusobacterium as compared to the healthy mucosa. Zhang, et al. revealed that Lactobacillus sp. A-2 metabolites have a probable role in the inhibition of growth and induction of apoptosis of human tongue squamous cell carcinoma.[3]

Conclusion:-

Both pathogenic and commensal strains of bacteria seem to play a role in oral carcinogenesis. 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. 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.

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