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Research Article

Role of Infectious Agents in Carcinogenesis

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Abstract-
There are infectious agents that play a significant role in carcinogenesis in no less than about 15% of cases and such carcinomas are associated with an infection by a specific pathogenic microorganism. A majority of infections that are carcinogenic usually present themselves as potentially modifiable risk factors, and thus, prevention tools already exist for them but are often not implemented. Human microbiome, is a microbiota with a collection of microbial taxa, of trillions of micro-organisms associated with humans and may have an advantageous or deleterious effect on their human host. Oral microbiome is of special significance owing to significantly high alpha diversity, many available niche with specific type of microbiome in each niche and significantly low beta diversity for individuals of a particular habitat. Longterm dysbiosis in any niche, leads to generation of primary & secondary metabolites by pathogenic microbes that, then cause, downstream effects from chronic infection & inflammation with presence of altered virulence factors and disruption of cell cycle and tumor signal transduction regulating cell proliferation and apoptosis as well as altered regulation of host immune response. These complex interactions then, lead to, not only oral carcinogenesis but also carcinomas of other areas of body due to, relatively unrestricted access of oral microbes to other parts of body directly or indirectly.

Keywords- Oral microbiome, Chronic infection, Chronic inflammation, Quorum sensing, Regulated cell death, Virulence factors

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Introduction

The cancers usually have an underlying random mutation, deletion, hypermethylation or hypomethylation of, the stem cell population that accounts for carcinogenic changes. In addition to these genetic alterations, the etiology is further complicated by the influences of hereditary and environmental factors. Besides, the known cancer-associated environmental risk factors like tobacco smoking, alcohol consumption, a high body-mass index (BMI), and exposure to ultraviolet radiation, there are infectious agents also, that play a significant role in carcinogenesis in no less than about 15% of cases and such carcinomas are associated with an infection by a specific pathogenic microorganism. These infections lead to poor oral hygiene that acts synergistically to enhance the risk of oral cancer. Bacterial infection is one of the major causes of chronic inflammation and it propagates tissue towards carcinogenic changes by themselves participating in metabolism of carcinogens and its subsequent phenomenae of facilitating increased cell proliferation, mutagenesis, oncogene activation, and angiogenesis that ultimately culminate in development of oral cancer (1-6)

A large majority of infection-attributable cancers have been seen to occur in less developed countries. In these countries, the infections seem to account for about one in four cancers. As a result of a series of insights into the perspective role of infectious agents in cancer over the past few decades it has been possible, to consider its etiological role and hence think about prevention of cancer with such etiologies. At present, more than ten infectious pathogens are classified as group 1 carcinogens by the International Agency for Research on Cancer (IARC) and among them, seven are viruses, three are parasites and there is a single bacterium known as Helicobacter pylori (H. pylori). From among these carcinogenic pathogens, the four with maximum number of carcinogenic associations to the development of carcinoma are Helicobacter pylori, High-risk human papillomavirus (HPV), Hepatitis B virus (HBV), and Hepatitis C virus (HCV). These four infectious agents when taken together, are seen to account for more than three-fourths of infection-related cancers worldwide. These prokaryotic microorganisms play a role not only in the development but also in progression of cancer. Contribution of carcinogenic infections to global burden of cancer requires periodic assessment. A majority of infections that are carcinogenic usually present themselves as potentially modifiable risk factors, and thus, prevention tools already exist for them but are often not implemented. Thus, greater awareness of health professionals as well as common public with stricter hygiene regimens as well as a strong public awareness protocol are necessary from the scientific community and public health organisations in order to reduce the propensity of carcinogenic infections. It is also essential to thoroughly evaluate through recent & proper scientific methods the associations between certain infectious agents and specific cancer subtypes and subsites. (2-5)

Human Microbiome

Microbiota is a collection of microbial taxa associated with humans and may have an advantageous or deleterious effect on their human host. It consists of trillions of microorganisms including bacteria, fungi, archaea and viruses inhabiting the particular host, In the human body, the number of bacterial cells are equivalent to, the number of human cells, however, the bacterial cells show a 100-fold higher genetic diversity of bacteria. Thus, bacteria elicit outstanding mechanistic and metabolic competences that influence not only their own microbial niche, but also host tissue–specific and immune cell functions. Owing to the insight available on constitution of a typical healthy microbiome due to the development and refinement of 16S rRNA sequencing techniques, alongwith studies such as the Human Microbiome Project (HMP), now, it also allows the analysis of the human microbiota in disease states. Additionally, it has helped to characterize the various properties of all bacterial communities of distinguished foci of human body in all states of health status, and has highlighted that, there is high interpersonal variability with regards to the composition of the microbiome and the makeup of the microbiota and so they differ greatly with anatomical location. So, certain taxa predominate at specific sites. Inspite of, a specific and distinctive makeup of each individual microbiome, the changes that occur in its composition are significant and hence can be broadly associated with disease states, thus, predisposing individuals to various diseases including cancers. (2,3)

Cancer promotion by microbial niche may occur due to various mechanisms as shown in Figure- 1.

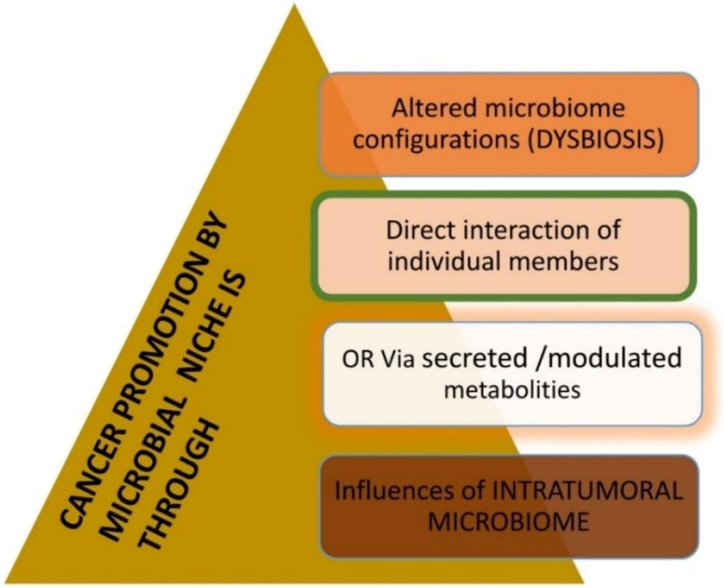

Figure 1-Modes of cancer promotion by microbial Niche

Oral Microbiome

The oral cavity and nasopharyngeal area have an environment which is moist and warm and so ideal for the growth of the microbiome. In these environments, pathogenic as well as mutualistic bacteria coevolve and hence, maintain homeostasis. In addition to the above-mentioned factors, the temperature of 37^0 C and pH of 6.5 to 7.5 in these cavities is also such that it allows establishment of a consistent environment for bacterial species. Besides all these, saliva also serves to cater to the nutritional needs of the microbial niche and keeps it hydrated.

The oral microbiome population changes in its composition with quality and quantity of saliva as well as, with change of site of oral environment (buccal mucosa, supragingival, and subgingival plaque) of oral cavity, but subsequent to the establishment of a bacterial habitat with both aerobic and non-aerobic bacteria in it, the biofilm thus formed does not allow changes in their environment. Oral cavity has numerous microbial habitats, which include both anatomical as well as pathological sites, such as, gingival sulcus, soft and hard palates, surfaces of teeth, buccal mucosa, tongue and periodontal pockets. The maximum range of variation of microbial colonies is seen in the tongue habitat of oral microbiota and the microbes by virtue of their presence on tongue, make provision for, the inhabitation by bacteria in other parts of the oral cavity by commuting in saliva. Fluctuations of microbial habitat environment facilitate the growth of pathogens, thereby aggravating the pathogenecity of those bacteria to cause oral diseases. (2)

The bacterial growth is also enhanced by the available nourishment of resident area because these nutrients promote and make it possible to create an oral environment favourable for the multiplication of bacteria present at that focus. Bacteria suspended in the saliva are most often entangled onto oral epithelial squames. Bacterial species of oral cavity are seen to react with specific response towards the varying and specific biological surfaces in the oral cavity of both hard and soft tissues. They are able to do so, by means of, various attachment sites and attachment molecules (adhesins) of microbes that facilitate their colony formation on various mucosal sites by means of "lock and key" mechanism suggesting a highly selective colonization site preference. The selective colonization, is further enhanced by, the availability of their respective and favourable attachment areas at the specific sites together with lessened defence abilities, consequently causing a change of oral microbial inhabitants towards the unfavourable pathogenic variety of microbiota spectrum in cancer patients. Therefore, communication between microbial cell surface attachment molecules, attachment area at a particular focus in an organism and gel-like cell environment serve as the primary reasons of, the oral biofilms' establishment phenomena. (2,1)

In the gingival region, oral biofilms first form in the region above the tooth covering mucosal areas and later on develop in the areas subjacent to gingival crevice as biofilms when a shift towards more pathogenic bacteria in the focal microbiome occurs and the bacteria of these two biofilms are significantly dissimilar. In the areas subjacent to gingival crevice, microbial colonies are predominantly made up of gram-negative obligate anaerobes. The initial colonization of teeth surfaces is however, by gram-positive aerobic bacteria, such as Actinomyces subspecies and oral Streptococci (S intermedius and S.oralis). (2)

Among all anatomical locations, the microbiome of oral cavity demonstrates the second highest level of alpha diversity (i.e. diversity within individuals) only next to that of the gut and hence, includes over 700 species of bacteria, over 100 species of fungi, and protozoa including Entamoeba gingivalis and Trichomonas tenax. As mentioned earlier, the oral cavity itself has many 'microhabitats', each with a unique microbiota composition. Surprisingly, however, the oral cavity exhibits very low levels of beta diversity when samples are taken from individuals living in the same areas, even in presence of a high intrapersonal diversity. The divergence in the constitution of the oral microbiota (i.e. dysbiosis) is attributable often to a coupled exposure to certain environmental factors, such as tobacco smoking, high-sucrose intake, and antimicrobial use.

The breakdown of dietary macronutrients (carbohydrates, proteins and fats) in the oral cavity by digestive enzymes supplied by host and microbial sources releases interlinked building blocks of these molecules that then permeate into oral biofilm, undergo further metabolism and release end products(primary metabolites) that impact the local ecology by allowing prevalence of certain bacterial species like sacchrolytic, acidogenic bacteria and dictate the nature of the relationship between oral coinhabitants, whether mutual or competitive. The most frequent secondary metabolites produced by the oral microbiota dysbiosis are the ribosomally synthesized and posttranslationally modified peptides (RiPPs) a bioactive polycyclic molecule & hybrid polyketide nonribosomal peptides (PKS-NRPs). By their presence they prevent the growth of other microbial competitor and improves colonization and oral biofilm formation. When the dysbiosis of the oral microbiota is such that it causes an imbalance and disturbs the homeostasis it promotes and facilitates the greater presence of potentially pathogenic microorganisms and thus leads to a number of intraoral and systemic diseases due to translocation of oral microorganisms. (3,5,9)

The translocation of these microbes occurs owing to:

a) interconnections between oral cavity and digestive as well as respiratory tract allowing freeway for their passage to these areas

b) Haematogenous & lymphogenous transmission attributable to traumatic events like tooth extraction. (1, 4)

The number of microorganisms ingested daily has been estimated to be more than thousand thus indicating that, from within the oral cavity, these ingested microorganisms have a relatively unconstrained access to the gastrointestinal tract as well as to a number of other organ systems. Therefore, dysbiosis of oral microbiota turns out to be an important bearing factor of the oral microbiota leading to its association with systemic diseases such as colorectal cancer, pancreatic cancer, Alzheimer's disease and cardiovascular disease. Another interesting finding is that, oral pathogens like Capnocytophaga, Veillonela & SARS Cov-2 tend to co-infect the lungs also. (3)

Relationship between Cancer hallmarks and oral microbiota

The development of cancer tends to show eight basic hallmarks of cancer as proposed by Hanahan & Weinberg. These include: sustaining proliferative signaling, the ability to

evade growth suppressors, resisting cell death, limitless replicative potential, the ability to induce angiogenesis and the activation of invasion and metastasis, the reprogramming of energy metabolism and the ability to evade immune destruction. Surprisingly, the oral microbiota-mediated carcinogenesis also goes through a majority of these hallmarks. One notable fact is that, the carcinomas with oral microbiota as their etiological factor are not limited to the oral cavity, but, oral microbiota-associated primary tumors have also been observed in the esophagus, stomach, pancreas and colon/rectum. Therefore, it is now known that, infectious agents increase the risk of cancer development in humans by various mechanisms which lead to induction & aggravation of chronic inflammation, genomic instability of affected cells with uncontrolled growth owing to disruption of cell cycle & tumor signal transduction, influencing host immune response with promotion of immunosuppression promoting cells and also interfering in the function of killer cells, besides inhibition of apoptosis and increase of cell immortalisation. These pathogenic microorganisms aggravate the situation further by indirectly metabolizing substances, including sulfides, nitrosamines, hydroxyl radical, acetaldehyde, deoxycholic acid and toxins, which then interfere with tumor occurrence, metastasis and recurrence. (2-7)

According to 2018 GLOBOCAN cancer incidence data, it had estimated for the first time incidence rates of infection-attributable cancer in 2018 at an individual country level. This, therefore will allow to raise awareness and inform recommendations for action against cancer, which tends to be viewed as a non-communicable disease. (8)

Multiple host cells of myeloid and non-myeloid origin possess cytosolic, membrane-associated receptors, and secreted pattern recognition receptors (PRRs) as well as NOD-like receptors (Nucleotide-binding Oligomerization Domain, NLRs), toll-like receptors (TLRs), RIG-I-like receptors (RLR), and C- type lectin receptors that may interact with periodontal microbial associated molecular patterns (MAMPs) [e.g., fimbriae, BspA (Bacteroides surface protein A), lipoproteins, lipopolysaccharide (LPS), nucleic acids] and hence, lead to damage/danger associated molecular patterns (DAMPs).(9)

Although there is evidence that, oral microbiota are playing a pivotal role in cancer formation, yet, the particular favoured foci of tissue areas for microbial migration and the underlying biological interactions of that phenomena at various far off foci still need to be proven. The demonstration of an integral interaction among the two paradigms of oral dysbiosis and tumor development has to be proven as yet. It will then, further aid in the development of new therapeutic anti-cancer strategies. (10)(Figure 2&3)

Evidence still suggests that periodontal pathogens can stimulate tumorogenesis by promoting epithelial cell proliferation and simultaneously inhibiting apoptosis by regulating the inflammatory microenvironment. Besides these, the candida organisms according to some researchers promote OSCC progression and metastasis through multiple mechanisms.(11)

Oral bacteria and their carcinogenic mechanisms:

The carcinogenic mechanisms mainly employed by oral bacteria include: (12-15)

a) Chronic infections
b) Quorum sensing
c) Chronic inflammation favouring overgrowth of certain commensals
d) Altered expression of virulence factors
e) Disruption of cell cycle and tumor signal transduction regulating cell proliferation and apoptosis
f) Indirect metabolizers of substances, including sulfides, nitrosamines, hydroxyl radical, acetaldehyde, deoxycholic acid and toxins, which interfere with tumor occurrence, metastasis and recurrence
g) Regulating host immune response

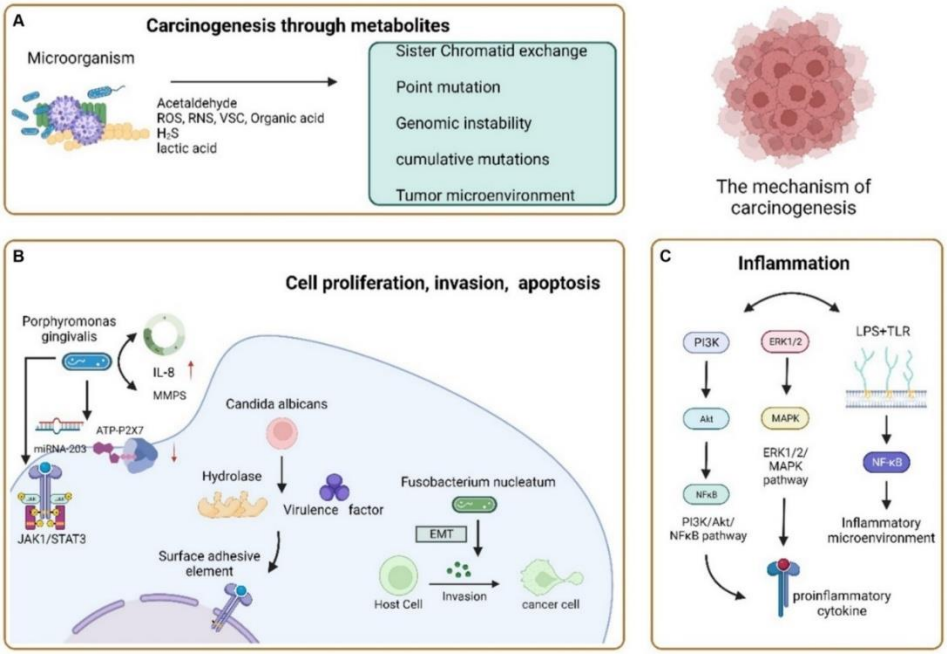

Figure 2- Microbial Carcinogenic mechanisms

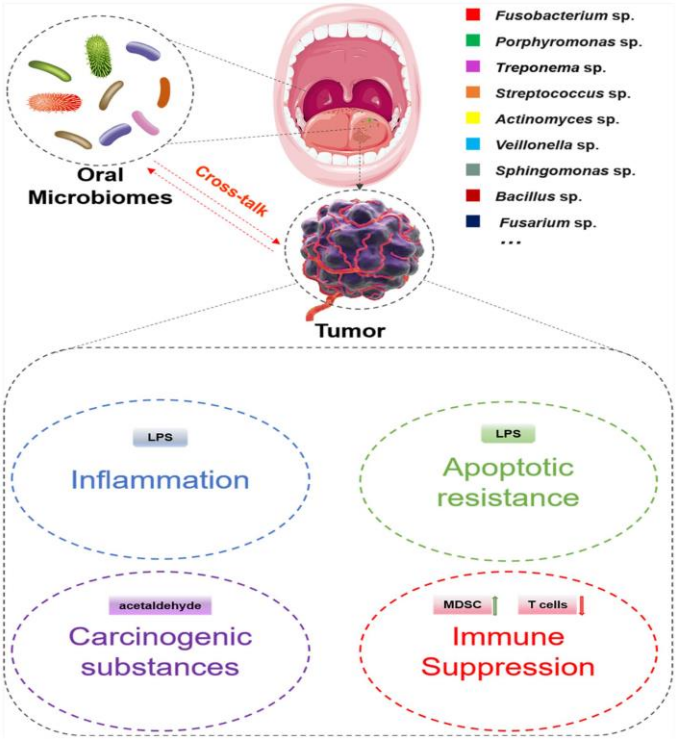

Figure 3-Oral microbiome and tumor crosstalk mechanisms

a) Chronic infection-

When an infection persists, cyclin D1 and mitogen-activated kinase (MAPK) pathways are activated, which leads to host cell proliferation and DNA replication. In such situations, due to a higher rate of genetic mutations present, these alterations in turn raise the chance of tumor development and the incidence of cell transformation.

At other times, the causative pathogens of chronic infection, destabilize the host cell signalling pathways, and thereby facilitate the survival of pathogens.

To compound these damages, the infectious agent frequently accumulates inside cells it has infected, which inhibits apoptosis mainly by changing the Bcl-2 family protein's expression or deactivating retinoblastoma protein pRb. This work module then, makes provision of a habitat wherein, the intrusion of pathogen into the host cell progressively goes on thus, ensuring bacterial sustainance even when there are endeavors of the inhabitation area defence system to knock down the infected cells by regulated cell death mechanisms. Ultimately, it facilitates the escapement of regulated cell death mechanisms by the alteration prone cells and paves way for their enhancement to a further stage of cellular modification to behave uncontrollably leading to malignant changes. (13)(Fig.-3,4 &5)

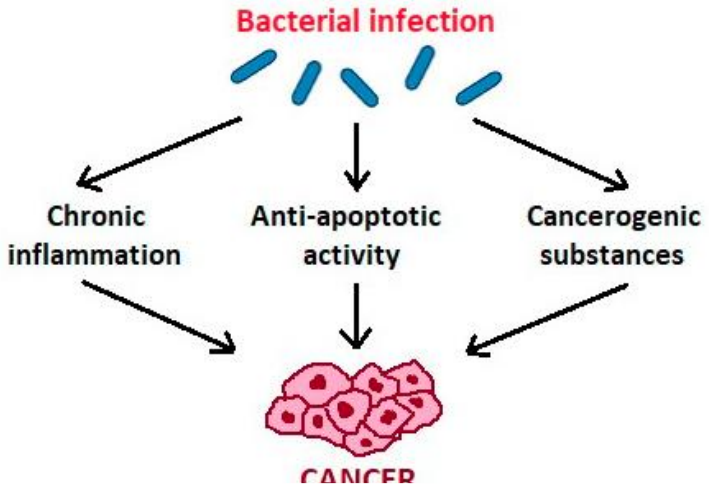

Figure 4-Reactive Tissue Phenomenae to bacterial Infections

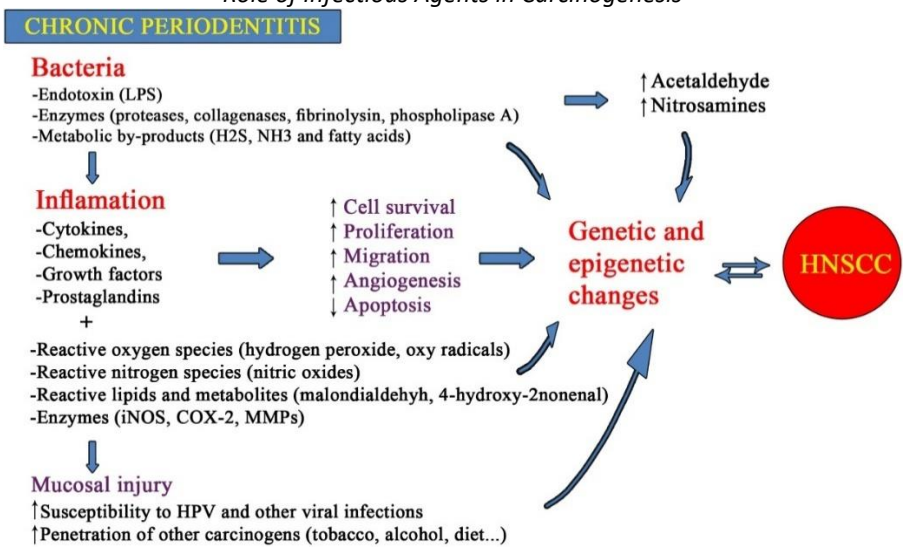

Figure 5- An insight on proposed role of chronic periodontitis in Head & Neck cancer

b) Quorum sensing –

When there is communication among bacterial cells by chemicals consequent to the expression of genes because of a high cell density, it's known as quorum sensing (QS). A mechanism like QS is required for the emergence of an oral biofilm because it promotes the coordinated and mutually beneficial behaviour of the bacteria and facilitates the formation of complex functional communities. Oral biofilms have been observed to be affected by quorum sensing molecules (QSMs) in multiple aspects including heme and iron absorption, virulence factor synthesis, stress-related gene expression, and proliferation. QSMs also indirectly affect host cells by transforming an oral biofilm's characteristics from a mutualistic state to a pathology-associated state.

Changes in the ratios of species populations and/or the expression of virulence factors, such as proteolytic activity, are recognized markers of this transition away from commensal biofilms. It's clear that oral bacteria use quorum sensing to synchronize gene expression and adapt to population density fluctuations. The mechanism of QS is responsible for the generation, release, accumulation, detection, and response to gene-activated signals. Gram-positive bacteria release small oligopeptide signaling molecules known as Autoinducer-2 (AI-2), which facilitates inter-species communication between Gram-positive and Gram-negative domains. (18)

c) Chronic inflammation favouring overgrowth of certain commensals-

Periodontal diseases are mostly caused by anaerobic oral bacteria, by triggering persistent inflammatory processes. These bacteria damage fibroblasts, endothelium and epithelial cells, and extracellular matrix constituents in addition to inducing the generation of inflammatory mediators. Consequently, the presence of periodontal infections raises the local concentrations of several cytokines for prolonged periods, including TNF-α, IL-6, IL-17, IL-23, and matrix metalloproteinases MMP-8 and MMP-9. Oral cancer risk is increased by a combination of factors including poor oral hygiene. Bacterial infection is a significant factor in the development of oral cancer as it leads to chronic inflammation, which in turn increases oncogene activation, mutagenesis, increased cell proliferation, and angiogenesis. Oral cancer is associated with a multitude of bacterial species. The graphic below elaborates on the interaction of released cytokines and their impact. (7)(Fig- 2,4, 5&6)

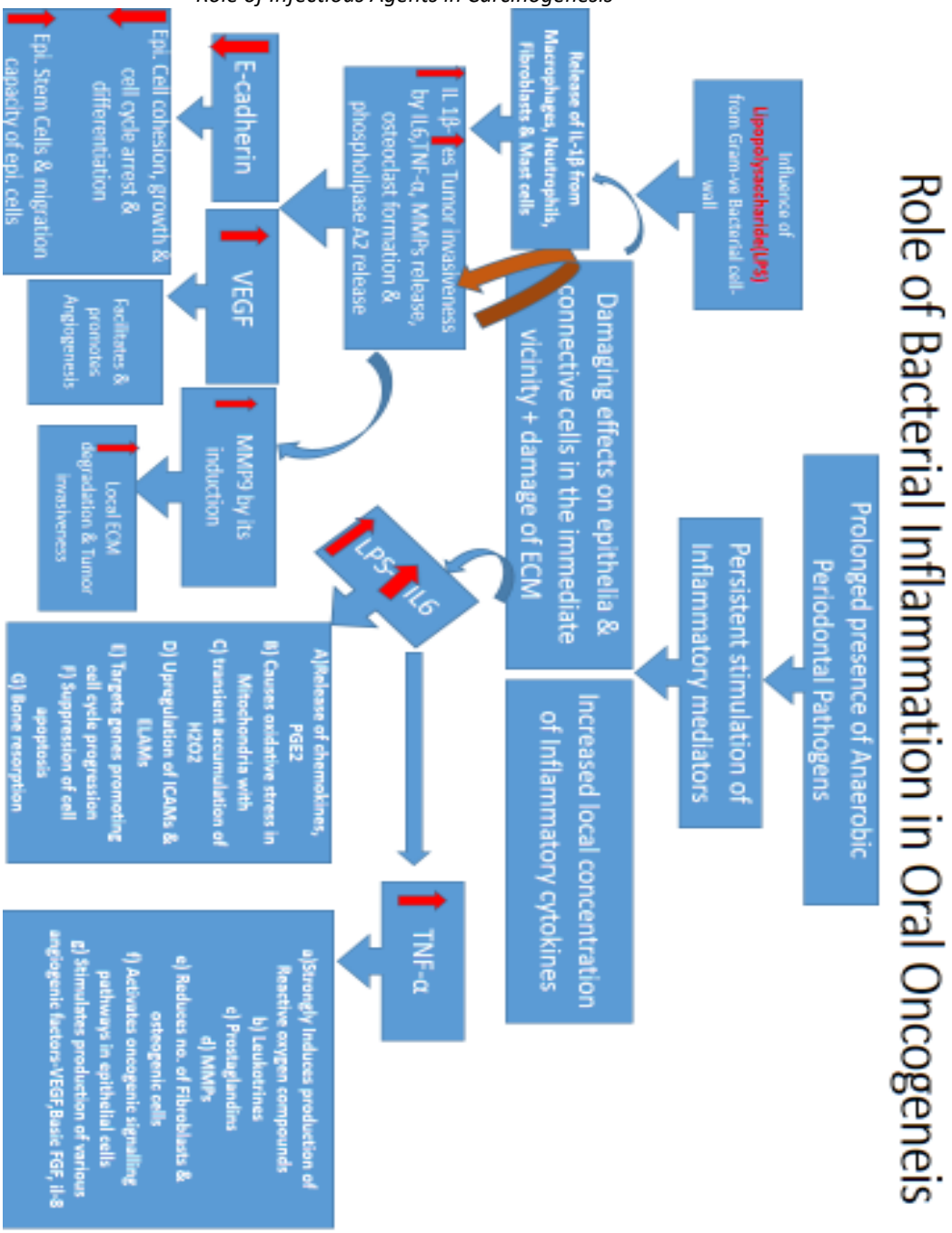

Figure 6-Schematic diagram of role of bacterial inflammation in oral oncogenesis

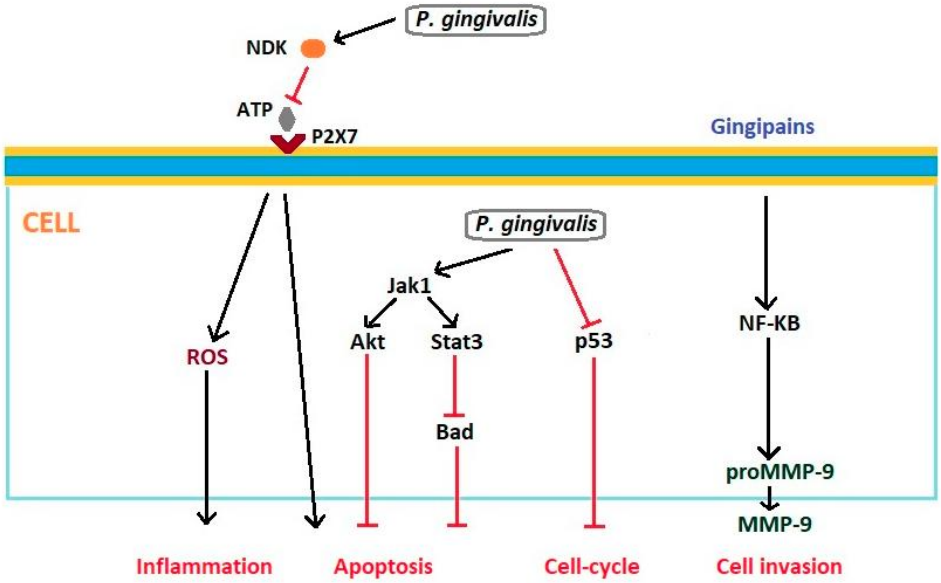

Figure 7- Mode of Anti-apoptotic Activity by P. Gingivalis on epithelial cells

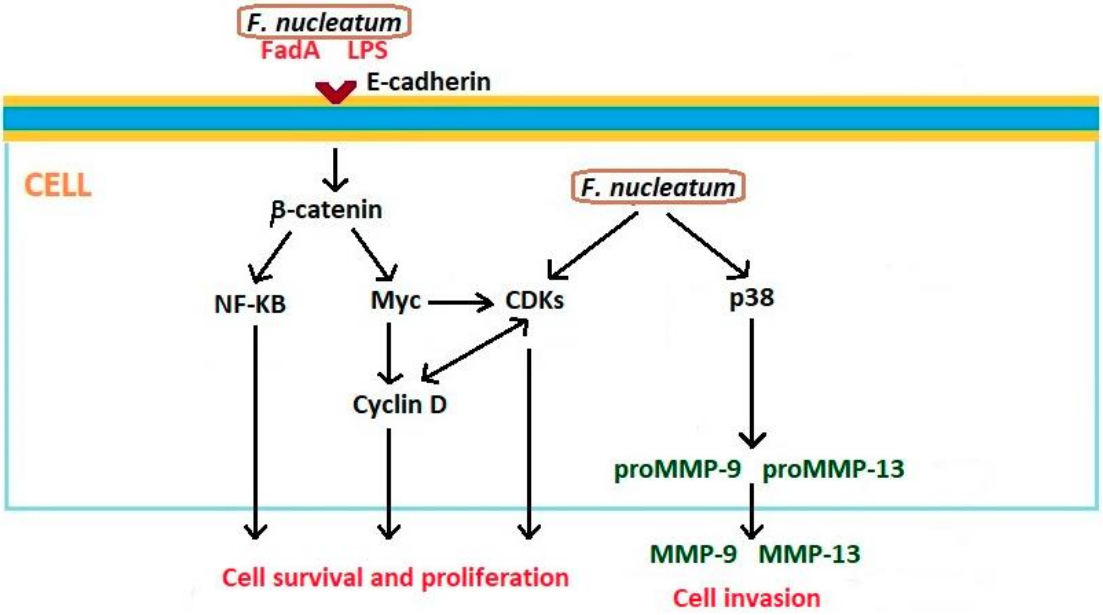

Figure 8- Mode of Anti-apoptotic Activity by F.Nucleatum for development of Oncogenic phenotype of epithelial cells

d) Altered expression of virulence factors- (6,16,17)
Subgingival microbiota, including Peptostreptococcus, Synergistes, Filifactor, Mycoplasma, and Olsenella, are the etiology of periodontitis. Some of these bacteria serve as keystone pathogens and others serve as accessory pathogens facilitating the virulence property of other pathogens. These pathogens cause altered expression of virulence factors in one of the following ways:

1. Potential periodontal pathogen Peptostreptococcus generates virulence factors like lipopolysaccharides (LPSs), peptidoglycans, lipoteichoic acids, and fimbriae adhesins which trigger the release of pro-inflammatory cytokines.
2. Additionally, P gingivalis also generates lipopolysaccharides(LPSs) that, stimulates osteoclasts and causes bone resorption. (Fig-7)
3. Other periodontal bacteria that produce a lot of virulence factors include A actinomycetemcomitans, P intermedia, T denticola, and N cinerea. Furthermore, it has been found that the microbiomes of periodontal disease display a significant prevalence of specific beneficial genes and metabolic processes, like bacterial chemotaxis, toxin synthesis, and flagellar assembly.
4. Researchers have shown that subgingival biofilms associated with periodontitis overexpress a few genes, including those linked to proteolysis, amino acid transport, iron acquisition, LPS production, and potassium ion transport. The microbial community's proinflammatory potential is subsequently enhanced by these metatranscriptomic modifications, and is evidenced by the fact that, there is boost in the production of pro-inflammatory cytokines by gingival epithelial cells

(GECs) coupled with a decrease in synthesis of human b-defensin 3 by them.

5. Furthermore, the interaction between periodontal microbial-associated molecular patterns and the cytosolic, membrane-associated receptors as well as secreted pattern recognition receptors (PRRs) of host cells promotes the growth, migration, and ulcerations of stratified squamous epithelium.
6. Due in large part, to their sticky nature, increased colonization by candida species is strongly correlated with oral epithelial dysplasia & its neoplastic transformation resulting in OSCC development.
7. Since F. nucleatum's proportions in oral biofilms related to both health and sickness are constant at roughly twenty-five percent, it is referred to as a core species in oral biofilms. Fusobacterium nucleatum plays a vital role as a "bridging" bacteria in the formation of dental plaque biofilm by co-aggregating with both early (Streptococcal spp.) and late invaders, including Porphyromonas gingivalis and thereby controls the architecture of the dental biofilm. By expressing adhesins like FadA and Fap2, it can bind and/or penetrate a variety of cell types, including T-cells, keratinocytes, macrophages, and oral, colonic, and placental epithelial cells.(Fig-8)

e) Disruption of cell cycle and tumor signal transduction regulating cell proliferation and apoptosis

The two categories of cell death that scientists have identified are controlled cell death (RCD) and accidental cell death (ACD).

I) When unintentional damage stimuli surpass a cell's capacity for adjustment, Accidental cell death (ACD) an uncontrollable process of cell death is initiated causing cell death to occur.

II) RCD, on the other hand, is the gene-controlled, self-organized & orderly death of cells. It guarantees the preservation of the interior environment's stability. The creation of signal amplification complexes, which are crucial for both immunological response and individual development in evolution, controls the induction and progression of RCD. Another name for RCD, which takes place in a physiological setting, is programmed cell death (PCD). The principal types of RCD that are currently understood are: **apoptosis, autophagy-dependent cell death, necroptosis, pyroptosis, ferroptosis, parthanatos, entosis, NETosis, lysosome-dependent cell death (LCD), alkaliptosis, and oxeiptosis**. When mammalian cells are subjected to irreversible disruptions in their extracellular or intracellular milieu, they may initiate one of several signal transduction pathways that ultimately result in their demise. There is a significant degree of interconnectivity among the molecular pathways that generate and propagate each of these RCD patterns. A wide range of morphological characteristics, ranging from total necrosis to total apoptosis, and immunomodulatory characteristics, ranging from anti-inflammatory and tolerance to promoting inflammation and immunogenicity, can also be seen in all types of RCD.

In general, RCD's crucial subroutines that could cause organelle disintegration or cell death due to cellular stress include apoptosis as well as autophagy-dependent cell death. (19)(Fig-9)

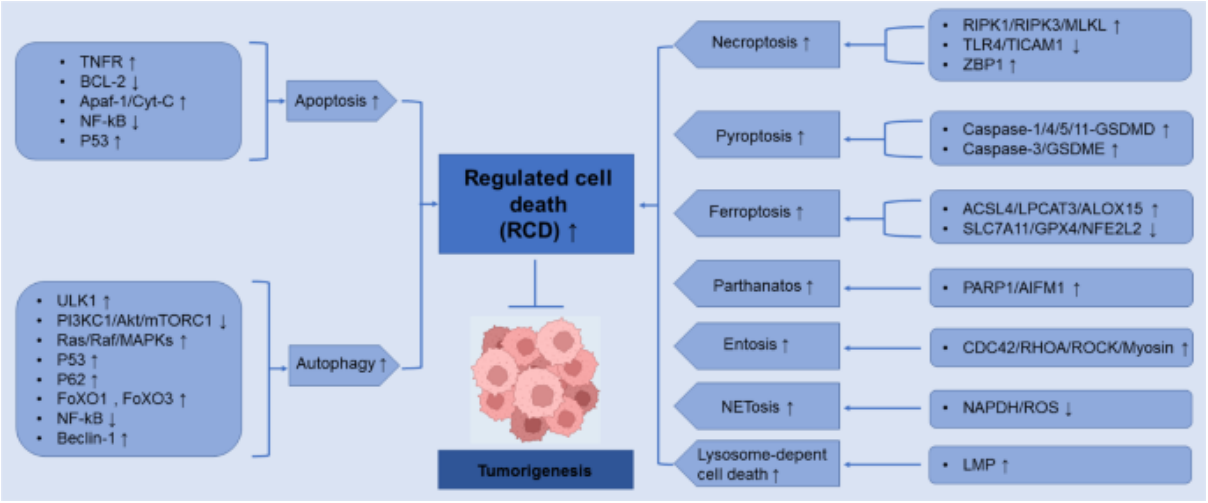

Figure 9-Types of regulated cell death and their molecules

Apoptosis- Cell cycle disruption is a prevalent characteristic of malignancies in humans. It is now known that apoptosis is an essential intracellular process that regulates cell population and preserves organism homeostasis. Through their anti-apoptotic properties and promotion of cell proliferation, oral bacteria aid in the development of cancer. Pro-apoptotic pathways are inhibited by the microbes such as P. gingivalis and F. nucleatum, which upregulate Cyclin D1 expression, downregulate p27, downregulate DNA repair proteins Ku70 and p53 along with pRb, or activate the COX-2/PGE2 pathway. They also cause the activation of anti-apoptotic signaling pathways. This duo of circumstances, often leads to the growth and survival of cancer. (21)

Through apoptosis, or programmed death, the body eliminates necrotic cells, however, interference with this process, can result in the formation of tumors.

Autophagy - Genes associated with autophagy control the autophagic process. Thus, harmful proteins or organelles can be broken down by autophagy, a phagocytic biological process that is necessary for preserving cell function and homeostasis through lysosomal fusion. It has been demonstrated that autophagy performs two antagonistic roles in the growth of tumors.

On one hand, when autophagy is inhibited in the precancerous stage, reactive oxygen species (ROS) build up and genomic malfunction occurs. These events together cause a rise in DNA damage and endoplasmic reticulum (ER) pressure, which aid in the development of tumors. Moreover, autophagy can provide nutrition and energy to tumors in response to oxidative stress or hunger, hence extending the survival of cancerous cells. While, on the other hand, autophagy-associated signaling pathways (e.g., Ras-"Raf-mitogen activated protein kinases (MAPKs), protein kinase B (Akt)-mammalian target of rapamycin complex 1 (mTORC1), and nuclear factor kappa-B (NF-κB) pathways) inhibit the metastasis and progression of tumors. (19)

Necroptosis-Receptor-interacting serine/threonine kinase protein (RIPK) 1 catalyzes" necroptosis, a regulated cell death mode, by forming complex IIB via its kinase activity. Its morphology is akin to necroptosis cells, and its signaling method is comparable to that of apoptotic cells. In this kind of RCD, the cancer cell contents that are discharged during cell rupture intensify the peripheral inflammatory response. Necroptosis differs from necrosis in that it exhibits active energy consumption and closely adheres to the regulation of intracellular signals in cancer.(19)

Pyroptosis- An inflammatory reaction is associated with pyroptosis, a type of PCD. Pyroptosis is mostly carried out by the Gasdermins family. (19)

Ferroptosis – A novel type of non-apoptotic, oxidative programmed cell death that has emerged recently is called ferroptosis. It differs from other cell death mechanisms in terms of shape, genetics, and molecular biology, including necrosis, autophagy, and apoptosis. Iron-dependent lipid peroxide damage to mitochondria, which leads to cell death, is a characteristic feature of ferroptosis. Additionally, glutathione peroxidase 4 (GPX4), an enzyme that repairs lipids, is not active in this condition. Its biochemical properties primarily manifest as an increase in nicotinamide adenine dinucleotide phosphate (NADPH) oxidation, which increases the production of lipid peroxidation products and ROS accumulation brought on by iron overload. It also inhibits the cystine/glutamate transporter system.

Ferroptosis is unique in that "the mitochondria shrink, the density of the mitochondrial membrane increases, the chromatin does not condense, the nuclear size is normal, the cell membrane is intact, the plasma membrane blisters, and the mitochondrial" cristae either disappear or diminish. Lipid peroxidation within cells is tightly controlled. Ferroptosis won't happen until this regulatory system is disrupted and lipid peroxide builds up to a fatal level. Ferroptosis incidence is significantly correlated "with the accumulation of iron in cells, production of free radicals, availability of fatty acids, and lipid peroxidation. (19)

Poly (ADP-ribose) polymerase-1 (PARP-1)-dependent cell death (parthanatos)- Another novel kind of regulating cell death is called poly (ADP-ribose) polymerase-1 (PARP-1)-dependent cell death (parthanatos). Parthanatos is not the same" as apoptosis or other forms of regulated necrosis. It is primarily shown by the fact that excessive amounts of par are produced when parthanatos arise due to aberrant activation of PARP-1. Parthanatos are commonly observed in a number of clinical processes, such as, damage caused by ROS, inflammatory inflammation and the development of tumors. The procedure will cause aberrant PARP-1 activation and result in the production of "several ADP ribose polymers (PAR) joined by glycosidic linkages. The substance par itself is harmful to cells. Parthanatos is thus primarily caused by the signal transmission of par polymer to mitochondria and the transport of AIF from mitochondria to the nucleus. Its" primary characteristic is that this procedure does not demand participation by caspase. (19)

Entosis- The RCD type that shows cell "cannibalism" is entosis. It is typified by intracellular cell structure wherein a single cell swallows up and kills another cell. Similar cells are phagocytized and eliminated following entosis activation via the lysosomal degradation pathway mediated by cathepsin B (CTSB) and LC3-related phagocytosis (LAP). Actin, myosin, RhoA, rock, cell adhesion, and cytoskeleton reorganizing are among the mechanisms that "regulate the induction of entosis. Along with cell adhesion and cytoskeleton rearrangement pathways, other signaling molecules and regulatory factors (including Cdc42) also contribute to the regulation of entosis in different ways". It is frequently observed in human tumor tissue and is described as a cell-in-cell (CIC) structure. (19)

NETosis- Histone citrullination and ROS generation mediated by NADPH oxidase govern NETosis, a type of RCD caused by neutrophil extracellular traps (NET). A type of inflammatory cell death is known as neutrophil extracellular traps or NETs. They are able to capture viruses, fungi, bacteria, and protozoa. DNA fibers, histones, and antimicrobial proteins make up the nets released by active neutrophils. Pathogens can be fixed by them and exposed to deadly amounts of effector proteins that are only locally present in the effector site. The process of neutrophils secreting nets is called NETosis. It is the neutrophils' inflammatory mechanism of cell destruction. The production of reactive oxygen species ("ROS), neutrophil elastase (NE) nuclear migration, myeloperoxidase antibody (MPO), histone modification, and chromatin degradation are the main processes involved in the formation of nets. The process of NETosis is dynamic and involves multiple signals and phases. NETosis mediates histone citrullination, which leads to chromatin deconcentration, nuclear membrane breakage, and chromatin fiber release. Within" the tumor microenvironment, nets are seen to form. The immune system's condition and the tumor microenvironment's interaction determine whether NETosis would have antitumor or tumor-promoting effects. (19)

Lysosome-dependent cell death (LCD)- It is also known as lysosomal cell death and is typified by lysosomal rupture that is mediated by hydrolase (cathepsin) or iron produced by lipoprotein polymerase (LMP). Thus, LCD is the consequence of exposure of cells to lysosomal detergent, dipeptide methyl ester, lipid metabolites, and reactive oxygen species (ROS) leading to rupturing off of lysosomes and consequent release of bulk of hydrolases. In LCD, cathepsin is a key component. LCD incidence can be decreased by inhibiting cathepsin expression or activity. (19)

One of the most important early warning signs of cancer is avoiding RCD. Consequently, controlling two or more RCD subroutines at the same time will be a viable cancer treatment approach.

f) Metabolizers of chemicals that indirectly interfere with the development, metastasis, and recurrence of tumors, by metabolizing substances such as sulfides, nitrosamines, hydroxyl radicals, acetaldehyde, and deoxycholic acid

It is possible for the bacteria in the oral cavity to produce a variety of carcinogenic derivatives through the metabolism of potentially carcinogenic substances by them. For example, they may convert ethanol into acetaldehyde, a carcinogenic derivative, to levels high enough to cause mutagenesis, DNA damage, as well as secondary hyperproliferation of the epithelium by the local microflora. (14) Numerous bacterial species and their strains, including Escherichia coli, possess the ability to catalyze nitrosation. Fungi and yeasts can also be considered nitrosating organisms. The, so- produced nitrosamine, seems to be a plausible candidate for esophageal cancer as well as carcinomas of other mucosal regions, including the oral cavity.

Not only is acetaldehyde (ACH) generated by mucosal alcohol dehydrogenases, but it can also be obtained in far larger concentrations owing to ethanol oxidation by the local oral microbiota. Compared to non-smokers, it is typically many times higher among smokers who have an alcohol problem. The International Agency for Research on Cancer has categorized ACH as a group I carcinogen. The DNA damage produced by ACH can result in a variety of mutagenic effects, including chromosomal defects, DNA adducts, DNA crosslinking, and aneuploidy. Improving oral hygiene in these people can reduce the amount of ACH generated, as oral microbiota are one of the primary sources of local ACH. (20)

g) Regulating of host immune response-

Anaerobic oral bacteria are more likely to accumulate in tumors due "to the anaerobic conditions present in the tumor microenvironment. By stimulating T and NK cells, forming intratumoral tertiary lymphoid structures (TLS), activating" the STING signaling cascade, and utilizing microbial-derived antigen presentation mechanisms, these intratumoral microorganisms have been shown to augment anti-tumor immunity. On the other hand, by increasing ROS levels, encouraging an anti-inflammatory atmosphere, compromising T cell function, and causing immunosuppression, they can also reduce anti-tumor immune responses.

The anaerobic conditions within the tumor microenvironment facilitate the accumulation of anaerobic oral microorganisms in tumors. These intratumoral microorganisms have been found to enhance anti-tumor immunity through activation of the STING signaling pathway, stimulation of T cells and NK cells, formation of intratumoral tertiary lymphoid structures (TLS), as well as microbial-derived antigen presentation mechanisms.

Conversely, they can also dampen anti-tumor immune responses by upregulating ROS levels, promoting an anti-inflammatory environment, impairing T cell function, and inducing immunosuppression. Aside from this, more immunosuppressive effects are associated with a reduction in cytotoxic T cells in areas where bacterial growth in tumors is higher.(Fig-2,5&6)

Role of oral microbiome in systemic cancers: (4)

The primary mechanisms that enable oral bacteria to translocate are as follows:

(i) Because of the structural connections between the respiratory tract, digestive tract, and mouth cavity, oral bacteria can enter these systems through food ingestion, inhalation of air, and saliva.

(ii) Hematogenous and lymphogenous transmission: distressing experiences, such as having a tooth extracted, may allow oral bacteria to infiltrate the bloodstream and cause distant metastases.

The development of systemic carcinoma essentially follows the same path: persistent infection with increased and prolonged colonization by pathogenic microbes is usually followed by persistent inflammation that damages host cells irreversibly and increases their sensitivity, which causes the cells to transform into cancerous ones.

Conclusion

Understanding the diverse microbial interactions that occur within the many distinct locations of the human microbiome, as well as the biochemical and molecular interactions that cause carcinogenesis in the microbiomes' occupants, is both crucial and imperative. The last several decades have seen a number of advances in our knowledge of the connections between infections and cancer, as well as growing opportunities for cancer prevention. In order to avoid these malignancies, it may be helpful to understand the carcinogenic pathways where these organisms play a key role. This can likely be done by using knowledge of the oral microbiome and infectious agents. Additionally, it might support the advancement of cancer treatments.

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