Review

Oral Microbiome Driving Chemical Carcinogenesis Dampening Therapeutic Outcomes

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Oral Microbiome Driving Chemical Carcinogenesis Dampening Therapeutic Outcomes

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Simple Summary

Previous reviews on oral microbiomes' role in developing oral squamous cell carcinoma (OSCC) neglects oral and non-oral-microbiomes interactions with host mucosa after responding to environmental pollutants. Furthermore, clinical trials routinely ignores microbiome roles in oncogenesis and treatment. This review provides detailed mechanisms concerning identification and evaluation of oral bacterial pathogens identified in brain, lungs, CRC, breast, cancers etc. and likely induce oral squamous cell carcinoma (OSCC). Environmentally derived nutrients and chemicals support survival of microbial colonies producing virulence factors, inflammatory, and metabolic-enzymatic agents, acting with endogenous synthesis of cancer-causing agents. Improved clinical study trial protocols require a better understanding of microbial roles in suppressing oncogenic therapies to reverse therapy failure and increase survival outcomes.

Abstract

Background: This narrative review evaluates bacterial pathogen dysbiosis support of host risk for oral squamous cel carcinoma (OSCC) mediating environmental exposomes. **Objective:** Review provides metabolic, enzymatic, and immunologic mechanisms of oral dysbiosis amplifying chemical carcinogenesis and suppressing therapies for cancer. **Narrative:** Oral dysbiosis engages with endogenous synthesis of tobacco specific N-Nitrosamines (TSNA) and degradation of tobacco leaf's poly-aromatic hydrocarbons (PAHs), and pollutants creating a reservoir of carcinogenic agent. Bacteria metabolism of essential amino acid tryptophan-tryptamine, PAHs and TSNAs amplifies chemical carcinogenesis risk for OSCC synthesizing ligands for aryl-hydrocarbon receptor (AHR) transcriptional environmental sensing. Lipophilic chemical affinities between bacteria and carcinogen facilitate intercellular aggregations and accumulations in oral epithelium. Gram negative bacteria's lipopolysaccharide (LPS) and endopeptidases enhance lipophilic peroxidation (e.g., trimethylamine oxide (TMAO), exciting pathogen pattern recognition responses (e.g., DAMP, PAMP) with toll-like receptor expression eliciting NF-KB transcription of cytokines, and pathogen's epoxide hydrolases of diol epoxides producing DNA adducts, mutations and oxidative stresses. LPS+PAH+TSNA causes lipophilic membrane disruption driving ubiquitination-proteosome and Golgi-trans network's inappropriate host protein degradation, sorting, and transporting of epithelial proteins. Pathogens adhere to epithelium and release bacterial virulence factors, (cysteine-serine) proteases, and endopeptidases. degrading immunoglobulins, complement, cytokines, and extracellular matrix increasing intracellular transcriptional complex expressions of proto-oncogene/oncogenes. Influence of arginine-polyamine-epigenetics-methylation, and nonessential (cysteine) amino acid, sulphuration suppresses oncology therapies. AHR derived E3 ubiquitin ligase enhances DNA instability, with biomolecular condensates supporting tumor microenvironment (TME). **Conclusion:** Oral bacterial oncogenesis results in evasion from immune recognition, depressed mucosal tumor immune surveillance, cytotoxicity and therapies.

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1. Introduction

2. Oral Dysbiosis Promotes Suppressing Therapy

There is increasing recognition that microbiome dysbiosis, pathogens, are subject to communicable exchange between people (e.g., SARS-CoV-2, periodontal bacterial pathogens). Continual exposure and infection foster pathogen survival, replication and redistribution to other tissues in the body. [1] Oral bacterial pathogens are identified in the blood stream, lymphatics, saliva, gastric reflux content, feces, breast milk and even tears [2,3]. These fluids and source sites not only increase continual exposure risk depending on concentration and virulence activity of pathogens but contribute to oral oncogenesis and non-oral oncogenic risks. It is important this review delves into oncogenic mechanisms to a greater extent than previous reviews.

Created in the oral cavity are niches-reservoirs of pathogens composed of biofilm governed by adaptation by pathogens also characterized by quorum sensing and extensive chemical communications. Thes niches form sites of opportunities for continual pathogenic exposures and oncogenic potential not only locally but to non-adjacent sites. [4] Variability in niche composition results from host immunologic (innate, adaptive), metabolic and physiological responses derived from oral epithelial cells, but also neural, endothelial, and salivary (adenomatous type) cells contribute factors.

All these cell types, when exposed continuously to pathogens, will show gradual decline in their maintenance and viability. Clinically we observe initial hyperkeratosis then atrophy, and then desquamation of squamous mucosal lining, desensitization, loss of salivary flow (xerostomia), dysgeusia and/or dysphagia.

Oral mucosal immunity also depresses overtime. Cell stress eventually produces immune exhaustion with autophagy and anergy. [5] We also recognize that oral bacteria actively cause immune suppressive activities produced by differentiation of T regulatory cells (CD4+/CD8+/CD25/ Foxp3+: T_{regs}) and immunosuppressive factors.

Bacterial metabolism is interposed into host metabolism and dietary resources. For example, green leafy vegetables provide essential amino acid, tryptophan, and bacteria mimic this with the tryptamine metabolic pathway. Both synthesize indole, and indoleamines as ligands for the aryl-hydrocarbon receptor transcription receptor complex (AHR-PAS-bHLH). [6] Diet derived indoleamine 2,3-dioxygenase (IDO) inhibition comes from sources of kynurenic acid or L-tryptophan. Environmental sensing complex participates in differentiation of T_{regs}. which synthesis immunosuppressive cytokines (e.g., IL-10, transforming growth factor beta (TGF-b) and cytotoxicity inhibitors (e.g., PD-1. LGA-3. CTLA-4) increasing risk for OSCC growth. [7] Inhibition of immunosuppressive cytokines can occur from high levels of IL-2, reducing transcription factors, autoantibody to CD25+ or Foxp3+ makers for Tregs, or presence of kinases inhibitors (e.g., phosphatase inhibitors (PP1), protein kinase C and Rho-kinase (ROCK) inhibitors of PP1-MYPT1; inhibitors of PP2A (SET/12PP2A/CIP2A). Lack of inhibition therefore suggests profound immune and non-immune cell disruption.

Bacterial pathogens also release endopeptidases, and proteases depressing immunity by degrading, immunoglobulin, complement, and disrupting CD80+/CD86+/B27+ antigen recognition along with activation of T cell immunoglobulin like mucin receptors (TIMS). [8] Taking together, oral bacterial pathogens produce profound depression in tumor immune surveillance. Both innate and adaptive immunity and cytotoxicity become compromised and if immunotherapy is administered under these conditions immune effective regulation is reduced. [9] Analytic assessment of these

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conditions when developing immunotherapy protocols is common and unaddressed as cause for less effective survival outcomes.

Bacteria pathogen's release virulence factors and toxins which may further reduce immune resistance (e.g., degradation of antibody, complement, immune cells) to pathogens, increasing bacterial pathogen survival and reduce host lysis of cancer cells. [10] Particularly, gram negative anerobic bacteria, suppress surgery, radiation, and chemotherapy treatments for OSCC. [11] Bacterial pathogens release a variety of endopeptidases. Metallo-matrix peptidases, Metallo-matric dipeptidyl-peptidases, (MMPs, DPP) disrupt extracellular matrix (ECM); degrade desmosome intercellular bridge networks, and host maintenance proteins. Enzymes release mimics (e.g., Subtilisin) of host transmembrane proteins (e.g. furin, serine endopeptidase, pro-protein convertase) to enhance adherence and endocytosis into epithelial cells. These enzymes deteriorate epithelial adherence to lamina propria proteins (e.g., adhesins, integrins, collagens) increasing desquamation and loss of protective mucosal lining allowing deeper infiltration of pathogens and carcinogens reaching stem cell, basal cells. In addition, pathogens adhere to tyrosine kinase receptor type, growth factor receptors (e.g., EGFR/PTEN/mTor) reducing the available levels of growth factors to accelerate primary and secondary epithelial retention and wound repair required for surgical closure also enhancing opportunities for pathogens to target basal stem cells.

Following endocytosis oral pathogens produce focal disorganization of lipophilic cell membranes and signal for intercellular transcriptional expressions (e.g., AHR-PAS-bHLH, HIF-1, NF-kB, ETS-1, AP-1, TP53, HRAS, etc.). Gram negative bacterial pathogens, Porphyromonas *gingivalis* (Pg) and Fusobacterium *nucleatum* (Fn), perio-pathogens, degrade host cell proteins (e.g., immunoglobulin, complement, degranulate perforin granules) but they also hijack host cell's ubiquitination-proteosome and Golgi network degradation system to target host membrane proteins. This results in inappropriate sorting and transporting of host membrane proteins with loss of normal cell function. [12,13] When this occurs with additional metabolic products (e.g., AHR-PAS-bHLH), glycation, arginine metabolites, or oxidative stress (e.g., ROS: nitrosyl radicals, superoxide anion, ferric-peroxyl radicals, and lipid peroxidation) there is DNA instability and mutations generated by oral pathogens contributing toward full malignant transformation.

Large portions of dietary nitrate is converted to nitrite by oral bacteria, creating a pool of nitrite in the mouth. Oral pathogens disrupt nitrosation cycling in the oral cavity (e.g., glycine derivatives) to create O^6-alkylating agents which are highly mutagenic forming GC-> AT transitions. Normally enzymes, O^6-alkylguanine-DNA alkyltranferase (MGMT overload) repair O^6-MeG however, in the presence of bacterial driven activity, O^6-carboxymethylguanine will accumulate. Overactivity in this system will produce more reactive agents, carcinogens (e.g., N-Nitrosamines) and DNA adducts. This system encourages DNA instability (adduct formations) and oxidative stress (e.g., AHR) with formation of antimetabolites (e.g., cationic peptides, anti-microbial peptides (AMP: histatins, defensins, lysozymes, lactoferrin), alkylating agents (e.g., SAM) and mitotic inhibition (e.g., ROS) sustaining more severe malignant transformation. These activities simulate chemotherapy and immunotherapy so with administration of exogenous chemo and immunotherapy further derangement of a symbiosis shifting toward dysbiosis. In addition, there is an endogenous capacity driven by oral pathogens (bacteria and fungi) to synthesize epoxide hydrolases, cytochrome P_{450} (CYP450: 1A1, heme monooxygenase); aldo-keto reductases (AKR) to create carbonyl radicals, and sulfotransferases unavailable allowing persistence of oxidized products. There is also a need for reducing agent function (cysteine) to reduce ROS, however, expression of glutathione-S-transferases usually provides protective control of ROS however this enzyme can become a source for reactive electrophiles consisting of epoxides, carbonium ions, and quinones. Bacterial nitro reductases function as part of nitrosation in the oral cavity resulting in synthesis of amides (secondary-tertiary) forming complexes with nitrites, nor-nicotine to form N-Nitrosamines and DNA adducts In addition, there are covalent DNA adducts (e.g., alkylated bases-O^6guanine and O^6-methylthymine) causing mutations and with exposure to tobacco-nicotine delivery systems, pyridyloxobutyl (POB) adducts

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(tobacco specific nitrosamines(TSNA) form adding on to continual burden for repair but increasing probable error.

Bacterial pathogens also reduce reepithelization, more endogenous alkylation (e.g., SAM) and inappropriate increased thrombospondin-1 (TSP-1), and microthrombi, increasing ischemia in tissues, with hypoxia inducible factor-1 (HIF-1) transcription promoting pathogenic replication for anaerobes. High HIF-1 transcription activity can assist with proto-oncogene expression related to PI3K/Akt expression driving hypoxia or stabilizing NF-kB (RELB, p50, p65/RelA) transcription of cytokines, with HIF-1a transcription. A reduction in bicarbonate (HCO3-) also occurs (metabolic acidosis) with widening ion gap and more polycationic accumulations affecting cell-to-cell intercellular bridge communications (e.g., desmosome adhesin complex molecules) inducing permeability, pore formation, expressing p38MAPK, phosphorylating and internalizing desmosomal cadherins (e.g., Dsg3) disrupting junctional complexes. Additionally, there is degradation of extracellular matrices (ECM) while DNA instability increases as a product of accumulating biomolecular condensates (e.g., histone-chromatin organization, assembly, aberrations, telomeric shortening (DNA damage response failures).

Together there is high degree of probability for less than robust chemotherapy, radiosensitivity and surgical repair.

Pathogenic infection produces receptor specific adherence to oral epithelial cells (e.g., heparan sulfate, toll-like receptors (TLR2,4), phosphatidylserine (PS), tyrosine kinase receptors (RTKs), lipophilic receptors sites LPS-phospholipids-arachidonic acid, etc…) to signal cytotoxic T Lymphocytes (CD8+CTLs) and oral γδTCR-T cells to the site, causing granzyme activity to produce release of perforin. However, with continual infection tumor immune effector cytotoxicity is diminished and transcriptional expression of proto-oncogene and oncogenes increases. These interactions suppress immunotherapy, possibly supporting depressed repair from radiation, chemotherapy, and surgery.

In contrast microbial compositions such as *Mycobacterium bovis* Bacillus Calmette-Guérin (BCG) can become useful as immunotherapy. This approach reported for bladder, oral or gastrointestinal cancers is thought to cause BCG to reprogram bone marrow hematopoietic stem and progenitor cells (HSPCs), leading to infection protection with remodeling of tumor microenvironment (TME). T cell-dependent anti-tumor responses, from monocytes, dendritic cells, and PMNs may synergize with checkpoint blockade·[14] However this approach is not evaluated in the presence of active oral infection. We suggest with persistent moderate to severe pathogenic gingival inflammation and reservoirs of pathogens a continuing immunosuppression, and oncogenic expression may overcome benefits from BCG administration.

Predominance and persistence of pathogenic species in biofilm-niches is composed of composed of both commensal and pathogenic microbes forming a complex ecosystem of adhesion and aggregations on oral epithelial cells surface . Bacterial pathogens enhance their adherence by using molecules of glycosaminoglycans, glycoproteins, phospholipids, soluble forms of PS, immunoglobulin, complement, and cytokines, all bathed by salivary proteins (e.g., albumin) and enzymes (lysozyme, lactoperoxides, amylases, histatins, cystatins) mixed with transudative proteins (e.g., serpins-plasminogen pro-activator). In addition, there are desquamated epithelial and salivary cells, and immune effectors, within this sea of bacteria, viruses, bacteriophages, transposons, exosomes, and multilamellar vesicles (e.g., blebbing membrane) unattached to epithelium or pathogenic targets. Together this composition diverts effective immune targeting of pathogens. Evasion from immune recognition by pathogen's incorporates sequestration in epithelium, epithelial lesions, and immune cells. Reservoirs of pathogenic colonies in biofilm, plaque, calculus can also disseminate to other sites of inflammation, and oncogenesis creating multiple sites in the oral cavity but also in non-oral sites.

Critically pathogens use their metabolism and enzymology to influence host cell's metabolism. This can include epigenetics methylation, acetylation and phosphorylation also affecting therapies. Bacterial enzymatic (e.g., arginase, arginine demethylase) input influences arginine metabolism, S-

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adenosyl-methionine (SAM) methylation to produce hypo or hypermethylation respectively silencing tumor suppressor genes while enhancing oncogene expression and evasion from immune tumor surveillance depressing cytotoxicity as cancer cell proliferate. [15]. These interactions require study as they may effectively reduce immunotherapy, chemotherapy, radiation, and surgery.

3. Dysbiosis Amplifies Environmental Exposome and Chemical Carcinogenesis

Oral bacterial pathogens respond to the presence of environmentally derived pollutants, chemical carcinogens and reactive chemicals from tobacco use, e-cigarettes and other tobacco-related products, and habitual use of alcohol consumption by producing endogenous synthesis of reactive carcinogenic compounds (e.g., N-Nitrosamines, reactive electrophiles). Young individuals that vape, increase their exposure to environmentally reactive chemicals and are high risk for periodontal disease while accumulating pathogens (**Figures 1 and 2**).

Figure 1. **Listing of Oral Microbiome and Environment Exposome Contributors**

Environment-Exposome	Oral Microbiome
1. Diet-Soil: Sources for Amino Acids Tryptophane (essential amino acid): Cruciferous vegetables (Brassica spp). Other: Assorted Foods-Vegetables and Fruits containing conditionally essential-non-essential arginine, and cysteine. **2.** Habits: Tobacco-smoke products and Alcohol use products (carcinogens, inflammatory) **3.** Smoke- Air-Water-Pollutants: Environmental protection agency of the US lists: chemical carcinogens, and the classes of these chemical structures include, poly-cyclic aromatic hydrocarbons, volatile alkaloids, aldehydes, reactive oxidative compounds, nitrosamines, heavy metals (e.g., Cr^{+6}), PFAS, Microplastics chemicals acting as endocrine disruptors, reactive gases, ionized particles (e.g., radiation), alkylating agents, and particulates.(**epa:https://www.epa.gov/haps/initial-list-hazardous-air-pollutants-modifications)**.	Viruses: (sRNA) Coronavirus, Enteroviruses (Piconoravirus); Flavivirus, Retrovividae, Orthomyxoviridae, Paramyxovirus, (dsDNA) Siphoviridae (Caudovirales), Miniviridae, Poxviridae, Human papilloma viruses, Herpesviruses, and Archaea (Bacteria like-eukaryote genome), Mobile genetic elements (MGEs) and transposons-casposons ("jumping-genes"). Bacteria: Oral Microbiome (Bacterial) Database reports 687 species,185 genera and 12 phyla. Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, Fusobacteria, Spirochaetes, Synergistetes, Chlamydiae, Chloroflexi,SR1, Saccharibacteria (TM7), and Gracilibacteria (GN02). Genera: Proteobacteria, Firmicutus, and Pseudomonas common in oral cavity *Thirty-two percent* of these species remain uncultivated, and about14% unnamed. *4-6% degrade PAHs (~27-41 species)*. *Smoker's Bacterial Genera:* Fusobacterium, Cardiobacterium, Synergistes, and Selenomonas, and genera for respiratory pathogens : Haemophilus and Pseudomonas species Fungi: *More than 85 oral fungal genera. 52 species (61.1%) degrades PAH.*

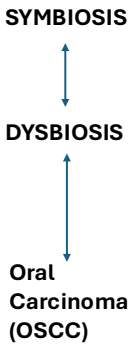

Figure 1. In brief we have provided a listing in two columns of the various components that are found in various environmental exposomes and the oral microbiome composition with inclusion of smoker's bacterial genera associations. There are active carcinogens, reactive chemical derivatives, irritant-charged particles, toxins, and habits that expose individuals to the array of agents listed above.

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Figure 2. **Environmental Influence on Selective Adaptive Oral Biofilm Microbiomes**

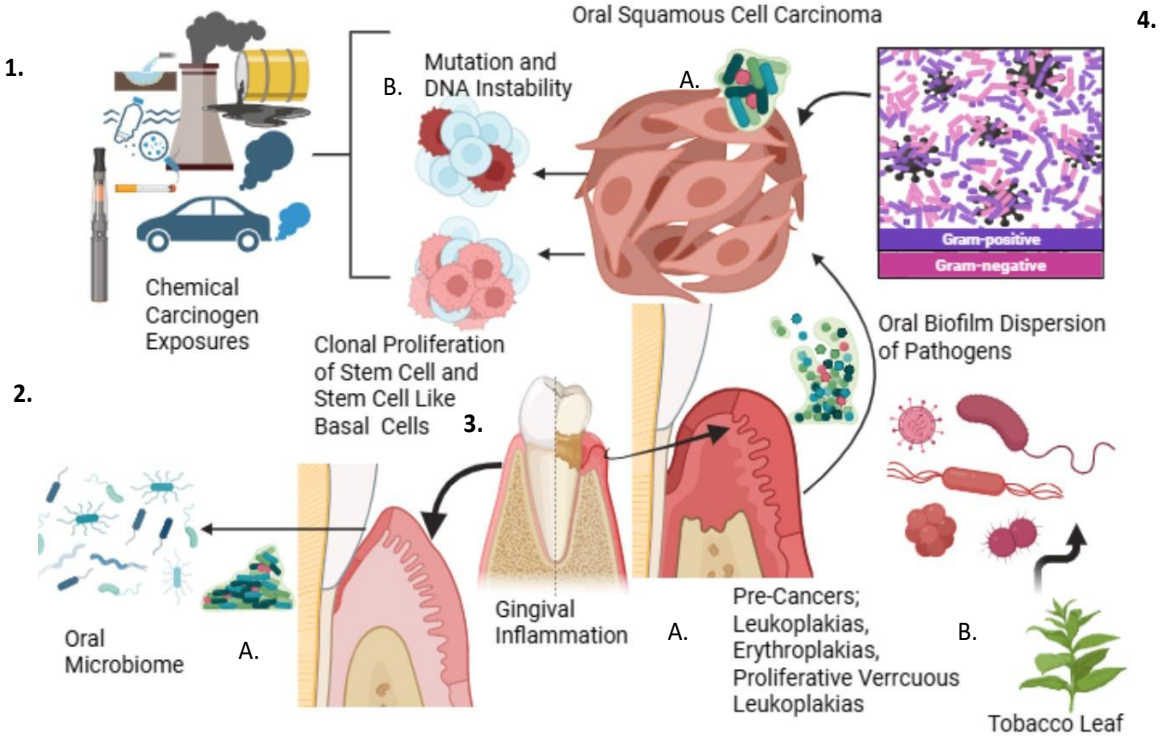

Figure 2. We show biofilm-plaques undergo continuous change as oncogenesis progresses from pre-cancer to established OSCC (**A**.). Additional interactions between the microbiome and malignant clones of basal epithelial cells and (**B**.) DNA instability and malignant cell proliferation results. We schematically depict oral oncogenesis in Figure 2., and the relationship between the environment and a variety of oral biofilms. In oral health, symbiosis biofilms are present, and the microbiome is promoting oral mucosal homeostasis (**2. A**.); oral mucosa immunity with tumor surveillance and cytotoxicity. Figure depicts exposure to environmental agents and the status of the oral microbiome to induce changes in gingiva resulting in morphology and functional loss of protective lining as inflammation persists. Shifting of oral microbiome from symbiosis sustaining mucosa to dysbiosis increases appearance of clinical pre-cancer lesions. Composition of this microbiome contains bacteria that can degrade tobacco leaf products such as poly-cyclic aromatic hydrocarbons (PAHs) and reactive derivatives as the bacteria express epoxide hydrolase and flavo-protein monooxygenases resulting in diol-epoxides and other reactive derivatives that can form DNA adducts and recreate DNA damages and mutations. This process is become disseminated as bacteria redistribute in the oral cavity to high-risk sites such as the lateral border of the tongue, floor of the mouth, buccal mucosa and vestibule where the basal cell populations are exposed as bacteria infiltrate int the stratum basilis, proliferative zone containing stem and stem cell like epithelial cells.

Our tables (**Tables 1 and 2**) and Figures **1 and 2** emphasize presence of environmental exposures coinciding with presence of oral bacterial pathogens producing metabolic and enzymology products disrupting host resistance to infection, depressing DNA stability, enhancing risk for mutations (e.g., DNA adducts) and loss of tumor surveillance immunity. [16] Within oral biofilms, although gram-positive bacteria are numerically dominant, gram-negative pathogens exert a disproportionately greater functional influence on host metabolism through release of virulence factors (e.g., outer membrane vesicle, fimbriae, and enzymes-proteases) Gram negative bacteria have a strong lipophilic compatible affinity to lipophilic compounds such as poly-cyclic aromatic hydrocarbons (PAHs). Release of expoxide hydrolases degrade PAH to more reactive diol-epoxides and then DNA adducts inducing mutations and promoting oxidative cellular injury.[17]

 doi:10.20944/preprints202603.1932.v1

Table 1. (A.B.) was developed through a series of searches. We filtered the initial 2,070 citations to 14 and evaluated the original identification of 99 bacteria and fungi through our oral filter to obtain 26 bacteria identified as present in the oral cavity with a capacity to degrade tobacco PAH but also identified by an OSCC, oral diseases or infection association (Table 1. A.B.). Our initial PubMed word search included: bacteria, PAH and degradation= 2,070 results. We then searched for bacteria PAH, tobacco degradation recording results= 14. Another word search with key words: adding oral term: gingival inflammation, resulted in 2 citations, and another word search with key words: additional oral term, resulted in only two citations. In another attempt using the term oral bacteria, combined with gingival inflammation, substituted by periodontal or periodontal disease with tobacco PAH degradation there were no results. The two cited studies; Tao et. al. (2024) and Ramano, et. al., (1999) investigated tobacco smokers, and presence of DNA adducts. Only Tao studied the presence of oral microorganisms. We performed another search to identify bacteria with PAH degradation capacity which were present in the environment and often linked with petroleum oil spills and PAH degradation. Search terms were combined using the Boolean 88 operators "OR", "AND", and "NOT". No restrictions were applied regarding the publication period recording research papers, reviews, and case reports. Filtering from 2,020 results our initial list of 99 bacteria was filtered to 26 bacteria, that were identified with degradation of tobacco leaf (e.g., fresh, cured, uncured, dry, moist, aged), and PAH. We reviewed this list again to assess whether any bacteria were identified as present in the oral cavity and oral cancer and recorded our findings in Table 1. A, B. which showed a positive relationship. Our conclusion was presence of oral cancers, gingival inflammation and virulent bacterial pathogens associated with PAH degradation is comparatively unaddressed in the oral microbiome compared to non-oral environment.

Table 1. A. Bacteria in Tobacco Leaf Possible Association with Oral Carcinoma and Other Diseases A.

Genera/Species	Association with Tobacco Leaf	Disease Association
(1) Acinetobacter spp	unburned cigarette tobacco leaf, loose-leaf chewing tobacco	pneumonia, bacteremia, arthritis periodontal-gingival inflammation
(2) Actinomyces spp.	aged flue cured tobacco leaf, loose-leaf chewing tobacco	root caries, periodontal –gingival disease,, skin abscess
(3) Atopobium parsvulum	unburned cigarette tobacco leaf	periodontal-gingival disease, halitosis, pelvic, abdominal abscesses,
(4)Bacillus pumilus	fermented fire-cured tobacco, ST products, cigarette tob., air-curing tobacco	severe pneumonitis, gingival disease,
(5) Citrobacter spp.	unaged and aged flue cured tobacco leaf	wounding ,enteritis, sepsis
(6) Clostridium spp.	unburned cigarette tobacco	neurotoxin, inflammation, colitis
(7) Corynebacterium spp	fermented fire-cured tobacco, nasal snuff, air-curing tobacco	chronic bronchitis, pneumonia, skin infection, surgical wounding, arthritis
(8) Curtobacterium spp.	aged flue cured tobacco leaf	infection, lymphadenitis, wounds, bronchitis,
(9) Dialister spp.	unburned cigarette tobacco	bacteremia, periodontal disease
(10) Enterococcus spp. *(gallinarum)*	unburned cigarette tobacco	endocarditis, UTI, pelvic infection, periodontitis-pulpal- gingival inflammation, oral mucosal lesions
(11) Escherichia coli	unburned cigarette tobacco	non-tumor mucosal lesions, enteritis, uremic infection gingival inflammation
(12) Firmicutes spp. (Bacteroides, oral clone BX005)	fermented fire-cured tobacco	mucin aggregation of bacteria, biofilm, periodontal -gingival disease, gastric C/
(13) Klebsiella spp	unburned cigarette tobacco	periodontal abscesses, pneumonia, arthritis
(14) Lactobacillus spp	fermented fire-cured tobacco	reduce infection or enhance selective increase infections, possible growth regulation of oral CA via lactobacillus *salivarius. (L. plantarum activate PTEN/mTor depressing MAPK.)*

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Table 1. B.
Bacteria in Tobacco Leaf Possible Association with Oral Carcinoma and Other Diseases

Genera/Species	Association with Tobacco Leaf	Disease Association
(17) Paenibacilllus spp (hodogayensis)	fresh and cured tobacco leaves, air-curing tobacco	mucosal neoplasia, (possible protective activity) polysaccharide-degrading enzymes antimicrobial
(18) Pseudomonas aeruginosa	unburned cigarette tobacco, dry and moist snuff	pneumonia, UTI, arthritis, osteochondritis, endocarditis
(19) Ralstonia spp	unaged and aged flue cured tobacco leaf	opportunistic infections, arthritis
(20)Rhizobium spp. (huautlense)	unaged flue cured tobacco leaf	oral inflammatory lesion, catheter infection, endophthalmitis infection
(21) Rhodococcus spp	unaged and unaged flue-cured tobacco leaf	brain abscess, encephalitis
(22) Serratia marcescens	unaged and aged flue cured tobacco leaf, air-curing tobacco	arthritis, nosocomial infections, catheter bacteremia, UTI, wound infections
(23) Sphingomonas spp. Bacterium	unaged and aged flue cured tobacco leaf	arthritis
(24) Staphylococcus spp (aureus)	unaged flue-cured, unburned cigarette leaf, loose-leaf chewing tobacco, dry and moist snuff	toxic shock, arthritis, food poisoning, periodontal and gingival inflammation
(25) Staphylococcus cohnii	fermented fire-cured tobacco, unburned cigarette	bacteremia, brain abscess
(26) Staphylococcus epidermidis	unburned cigarette tobacco , moist and dry snuff	constitutive on skin, nosocomial infection

Table 2. (A.B.) we provide a list of oral bacteria, mostly harvested from a variety of pre-cancer and established oral carcinoma lesions or via sampling of saliva. We cite peer-review studies and reviews that recognize unique microbiomes in lesions of pre-cancer and established OSCC, or salivary samples compared from intralesional sampling of oral carcinoma. However, there is usually insufficient detail, and largely a listing of bacterial genera in lesions or in saliva; with few studies providing species and still fewer attempting to use referred biochemical pathways to provide a landscape of bacterial pathogenic molecular, metabolic, physiologic, and immunologic activities contributing to oral malignant transformation. Moreover, metabolic and enzymology generated by oral bacteria, is also largely overlooked. We noted above, oral pathogenic bacteria such as F. nucleatum or Pseudomonas aeruginosa, capable of PAH degradation activity, are interactive with host oral mucosa. They are also under influence by oral virus (e.g., Siphoviridae) receiving via bacteriophage (e.g., lytic phage FNU1, Fnp⊙O2), transposons, or caposomes genetic information, disrupting their biofilms, promoting antibiotic resistance and survival in a shifting dysbiotic ecosystem but also offering an avenue to control potential bacterial driven oncogenesis. [50,51] Furthermore, current discussions of environmental exposomes also largely neglect microbiomes, especially oral although gut microbiomes are included. Thus, there is a lack of attention to discuss oral to gut bidirectional inflammatory axis. In Table 2. (A.) we categorized pre-cancers: leukoplakia (homogeneous (HL), dysplastic (irreversible) proliferative verrucous (PVL) lesions and OSCC with intralesional bacteria identification cited from the literature. We include for comparison Table 2. (B.), citations, and whether samples were from saliva or lesions for harvesting of oral bacteria.

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Table 2. A.	Bacteria Species Associated Pre -cancer and Established OSCC	
Origin of Identification	Identification of Oral Bacteria (Species)	Cited Study Results
Leukoplakias (homogenous, HL)	Streptococcus parasanguinis, Streptococcus salivarius, Fusobacterium periodonticum, Prevotella histicola, Porphyromonas pasteri, and Megasphaera micronuciformis.	Herreros-Pomares A, Hervás D, Bagan-Debón L, Jantus-Lewintre E, Gimeno-Cardona C, Bagan J. On the Oral Microbiome of Oral Potentially Malignant and Malignant Disorders: Dysbiosis, Loss of Diversity, and Pathogens Enrichment. Int J Mol Sci. 2023 Feb 9;24(4):3466. doi: 10.3390/ijms24043466. PMID: 36834903; PMCID: PMC9961214
Proliferative verrucous leukoplakia, (PVL)	Prevotella salivae, Campylobacter concisus, Dialister pneumosintes, and Schaalia odontolytica.	Herreros-Pomares A, Hervás D, Bagan-Debón L, Jantus-Lewintre E, Gimeno-Cardona C, Bagan J. On the Oral Microbiome of Oral Potentially Malignant and Malignant Disorders: Dysbiosis, Loss of Diversity, and Pathogens Enrichment. Int J Mol Sci. 2023 Feb 9;24(4):3466. doi: 10.3390/ijms24043466. PMID: 36834903; PMCID: PMC9961214
Severe dysplastic leukoplakias	*Rothia mucilaginosa Leptotrichia* spp. and *Campylobacter concisus*	Amer A, Galvin S, Healy CM, Moran GP. The Microbiome of Potentially Malignant Oral Leukoplakia Exhibits Enrichment for *Fusobacterium, Leptotrichia, Campylobacter*, and *Rothia* Species. Front Microbiol. 2017 Dec 1;8:2391. doi: 10.3389/fmicb.2017.02391. PMID: 29250055; PMCID: PMC5717034
OSCC (lesion)	Capnocytophaga leadbetteri, Capnocytophaga sputigena, Capnocytophaga gingivalis, Campylobacter showae, Metamycoplasma salivarium, and Prevotella nanceiensis	Herreros-Pomares A, Hervás D, Bagan-Debón L, Jantus-Lewintre E, Gimeno-Cardona C, Bagan J. On the Oral Microbiome of Oral Potentially Malignant and Malignant Disorders: Dysbiosis, Loss of Diversity, and Pathogens Enrichment. *International Journal of Molecular Sciences*. 2023; 24(4):3466. https://doi.org/10.3390/ijms24043466
Proliferative Verrucous Leukoplakia (PVL)-OSCC	Lachnospiraceae bacterium, Selenomonas sputigena, and Prevotella shahii.	Herreros-Pomares A, Hervás D, Bagan-Debón L, Jantus-Lewintre E, Gimeno-Cardona C, Bagan J. On the Oral Microbiome of Oral Potentially Malignant and Malignant Disorders: Dysbiosis, Loss of Diversity, and Pathogens Enrichment. Int J Mol Sci. 2023 Feb 9;24(4):3466. doi: 10.3390/ijms24043466. PMID: 36834903; PMCID: PMC9961214. Intini R, Balsells S, Bagan L, Fortuna G, Sroussi H, Bagan J. Comparative analysis of oral microbiome in saliva samples of oral leukoplakia, proliferative leukoplakia and oral squamous cell carcinoma. Front Oral Health. 2025 May 14;6:1600090. doi: 10.3389/froh.2025.1600090. PMID: 40438084; PMCID: PMC12116504

Table 2. B	Bacteria Species Associated Pre -cancer and Established OSCC	
Origin of Identification	Identification of Oral Bacteria	Cited Study Results
Salivary Samples for OSCC	Capnocytophaga gingivalis, Prevotella melaninogenica, Streptococcus mitis, Fusobacterium periodonticum, Prevotella tannerae, and Prevotella intermedia	Pignatelli P, Romei FM, Bondi D, Giuliani M, Piattelli A, Curia MC. Microbiota and Oral Cancer as A Complex and Dynamic Microenvironment: A Narrative Review from Etiology to Prognosis. Int J Mol Sci. 2022 Jul 28;23(15):8323. doi: 10.3390/ijms23158323. PMID: 35955456; PMCID: PMC9368704
Saliva Sample (2)	Prevotella melaninogenica, Fusobacterium sp., Veillonella parvula, Porphyromonas endodontalis, Prevotella pallens, Dialister, Streptococcus anginosus, Prevotella nigrescens, Campylobacter ureolyticus, Prevotella nanceiensis, Peptostreptococcus anaerobius	Rai AK, Panda M, Das AK, Rahman T, Das R, Das K, Sarma A, Kataki AC, Chattopadhyay I. Dysbiosis of salivary microbiome and cytokines influence oral squamous cell carcinoma through inflammation. Arch Microbiol. 2021 Jan;203(1):137-152. doi: 10.1007/s00203-020-02011-w. Epub 2020 Aug 11. PMID: 32783067
Saliva sample (3)	*Streptococcus anginosus, Abiotrophia defectiva, and Fusobacterium nucleatum and reduced Prevotella-histicola, Haemophilus*-parainfluenzae, *and Fusobacterium*-*periodonticum*	Han Z, Hu Y, Lin X, Cheng H, Dong B, Liu X, Wu B, Xu ZZ. Systematic analyses uncover robust salivary microbial signatures and host -microbiome perturbations in oral squamous cell carcinoma. mSystems. 2025 Feb 18;10(2):e0124724. doi: 10.1128/msystems.01247-24. Epub 2025 Jan 28. PMID: 39873508; PMCID: PMC11834404
Healthy Saliva	175 bacterial species comprised the bacterial flora of human saliva, including bacteria known to be commensal human flora but also Haemophilus *influenzae*, Neisseria *meningitidis*, Streptococcus *pneumonia*e, and Gamma proteobacteria.	Hasan NA, Young BA, Minard -Smith AT, Saeed K, Li H, Heizer EM, McMillan NJ, Isom R, Abdullah AS, Bornman DM, Faith SA, Choi SY, Dickens ML, Cebula TA, Colwell RR. Microbial community profiling of human saliva using shotgun metagenomic sequencing. PLoS One. 2014 May 20;9(5):e97699. doi: 10.1371/journal.pone.0097699. Erratum in: PLoS One. 2014;9(8):e106124. PMID: 24846174; PMCID: PMC4028220.
Smokers:Saliva Lower abundances of	*Streptococcus sanguinis*, *S. parasanguinis*, *S. oralis*, *Granulicatella elegans*, *G.*	Lee YH, Chung SW, Auh QS, Hong SJ, Lee YA, Jung J, Lee GJ, Park HJ, Shin SI, Hong JY. Progress in Oral Microbiome Related to Oral and Systemic Diseases: An Update. Diagnostics (Basel).

The oncogenic potential of pathogens derived from gingival inflammation and oral biofilms is further amplified by adherence and invasion into oral epithelial basal and stem-like cells, while simultaneously transporting environmental pollutants such as polycyclic aromatic hydrocarbons (PAHs), N-nitrosamines, and microplastics into the very cells under infection attack.[18] These processes aid initiation and promotion stages of carcinogenesis, and produces membrane receptors signaling (e.g. heparan sulfate, transmembrane, phosphatidylserine, toll-like, tyrosine kinase, G-protein-calcium dependent receptors) and induction of transcription to synthesis cytokines and produce proto-oncogene and oncogene expressions.

Oral bacterial pathogens behavior may be controlled by oral viruses, enhancing oncogenic potential through genetic instructions transmitted via bacteriophages and other mobile genetic elements. [19] In biofilm, bacterial pathogens respond to quorum sensing to disrupt networks sustaining pathogen dominance and establish biofilms as long-term reservoirs supporting oncogenic activity.[20] Public genomic database analyses support these associations. If we concede presence of bacterial pathogens in oral squamous cell carcinoma (OSCC) reflects sustained interactions, we note

 doi:10.20944/preprints202603.1932.v1

several oncogenic genes significantly altered in expression in OSCC compared with normal tissues. For example, the aryl hydrocarbon receptor (AHR) shows statistically significant differential expression (ANOVA $p = 4.0 \times 10^{-2}$) in OSCC.[21] Intercellular genomic and molecular interactions driven by presence of bacterial pathogens sustain not only malignant epithelial transformation, but degradation and remodeling of extracellular matrix (ECM) and development of the tumor microenvironment (TME).

Key bacterial species, including *Pg*, *Fn*, and *Treponema denticola (Td)*, are consistently associated with periodontal disease and oral cancer. Along with *Streptococcus*, *Actinomyces*, and other genera taxa (**Table 1**), they show capacity to degrade tobacco leaves and related products, sustaining elevated levels of PAHs and N-nitrosamines in the oral cavity. We noted above, endogenous nitrites, amides, nicotinic acid, epoxide hydrolases, dehydrogenases, and virulence-associated proteases (e.g., cysteine proteases) function together to contribute to reactive chemical and DNA adducts. Together pathogens amplify responses to environmental exposures enhancing DNA instability, mutations as oxidative stress and oncogenic molecular pathways express. [22,23]

Carcinogenic chemicals include PAHs, N-Nitrosamines, volatile alkaloids, aldehydes, and alcohols, which are functionally subject to bacterial metabolism through cytochrome P_{450} oxidative metabolism and AHR transcriptional complex (AHR–ARNT–PAS–bHLH), acting as an environmental sensing system. Activation of this complex leads to nuclear translocation and induction of epigenetics (e.g., methylation), including E3 histone ligases, resulting in chromatin reorganization and altered transcriptional responses to DNA damage in epithelial stem cells susceptibility to microbial enzymology and environmental chemical exposure (**Table 1, Figures 1 and 2**).

Bacteria lack their own AHR complex, but they do possess alternative sensing systems, including two-component regulatory systems and quorum sensing networks, enabling detection of environmental chemicals and regulation of virulence factor expression [24]. Along with oral viruses' contribution of bacteriophages and transposons, altering bacterial adherence, survival strategies, increasing oncogenic risk.[25] In health, microbial symbiosis maintains commensal species supporting epithelial homeostasis and immune surveillance. These microbes promote resistance to pathogenic colonization, stimulate mucosal immunity, and facilitate rapid immune effector responses. Oral immune factors including lysozyme, lactoperoxidase, perforin, and granzyme, exert bacteriostatic and cytotoxic effects suppressing malignant transformation [26–28]. However, with dysbiosis and loss of bacteriostatic and bactericidal enzyme activity and additional environmental exposome including tobacco, marijuana smoke, industrial pollutants, and microplastics a disruption of microbiome and mucosal equilibrium occurs. Chemical agents parallelling pathogen accumulation in the oral cavity, (**Figure 2**.) may suppress tumor immune surveillance increasing differentiation of T_{reg}s, generating oxidative stress, and oxidation induced DNA instability, promoting epigenetic reprogramming for tumor suppressor genes and oncogenes. [29,30]

Histopathology, organization, and tissue architecture of oral epithelium contributes to biofilm organization and presence of pathogens by providing nutrient resources, enzymatic resistance (e.g., lysozyme) to select bacterial survivors while maintaining proper colony growth, an adherence platform, and an intercellular sequestration site, forming an immune evasion reservoir. High-risk anatomical sites such as the lateral border of the tongue and floor of the mouth can be sites for preferential deposition of carcinogens because these sites are inherently weak compared to low-risk sites (e.g., palate) and relatively easily infiltrated by microbes with carcinogens piggy-backing and acting as a Trojan-Horse enhancing chemicals and pathogen accumulation in oral epithelium. Moreover, due to airflow dynamics, continual exposure of epithelial structure, reduces barrier function, elevating DNA adduct burden and stem cell vulnerability at these sites. [31,32]

4. Oral Bacterial Pathogens Regulate Arginine, Methionine and Therapy

Pg, Fn, Td and the "red-complex" aggregations form biofilm and enter cells consuming and depleting arginine reduces T-cell activities such as antigen recognition, and cytotoxicity, with

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immunosuppression and reduces effective oncology therapies. [33] Periodontal pathogens are contributing to progression of periodontitis by manipulating the same host immune responses needed to control malignant transformed cells. This includes metabolism of arginine, depletion by expression of arginase-1 (ARG1) which normally helps regulate inflammation. [34] Periodontal pathogens disrupt host homeostasis, promoting a pro-inflammatory environment enhancing arginase-1 expression in pre-cancer and epithelial cells undergoing malignant transformation by periodontal pathogen. Thus, arginase-1 increased expression in OSCC reflects severity of gingival inflammation. [35] Depletion of arginine, and reduction in tumor immune surveillance and cytotoxicity impairs T-cell and NK-cell function. Arginine deprivation downregulates the T-cell receptor (TCR) CD3ζchain, hindering T-cell activation but producing anergy, proliferation, and cytokine production (interferons). [36] ARG1 enzyme is overexpressed not only in OSCC but in other tumors and myeloid-derived suppressor cells (MDSCs). [37] Elevated serum ARG1 activity compared to healthy individuals, indicates progression of tumor and oral chemical carcinogenesis. [38,39] Elevated ARG1 in plasma exosomes is linked to metastasis, acting as a potential prognostic marker. [40] Arginine scarcity also identifies periodontal pathogens immune evasion, because of T/NK depleted functions, but also reduction of immunotherapy, radiation, chemotherapy, and post-surgery immune recovery. Assessment of oral pathogen presence, with ARG-1 detection could aid pre and post therapy for OSCC.

Moderate to severe gingival inflammation contains pathogens consuming arginine. Significance expands to include arginine related epigenetics, alkylating agent S-sadenosylmethionine, SAM methylation (SAMe), that generates adducts: N^7-Methylguanine (N^7-MeG) and N^3-methyladenine (N^3-MeA) via Sn2 mechanism and is linked to methionine and disruption of polyamine synthesis and B complex vitamin activities. These include folic acid, citrovum (leucovorin or folinic acid, rescue needed for methotrexate chemotherapy treatments) for OSCC. [41] The methionine cycle produces SAMe, linkage to folate cycling (one-carbon metabolism) via methionine synthase, which requires 5-methyltetrahydrofolate (5-MTHF). Reduced folate levels decrease regeneration of methionine from homocysteine, leading to decreased SAMe synthesis and reduced DNA methylation (global hypomethylation). This causes genomic instability and activates proto-oncogenes and/or DNA methylation (both global hypomethylation for oncogenes and local hypermethylation, silencing tumor suppressor genes) regulating tumor suppressor and oncogene expressions in OSCC initiation and progression. [42] SAM levels rise in OSCC following radiation therapy (RT), enhances DNA repair mechanisms and contributes to radiation resistance. [43] Targeting SAM synthesis (specifically using MAT2A inhibitors) or manipulating methionine metabolism to reduce SAM levels is a potential strategy to increase the efficacy of radiation in solid tumors after consideration of the oral bacterial pathogen contribution. Bacterial pathogens can help to maintain SAM and reverse therapy for oral carcinoma. Bacterial pathogens actively maintain high levels of SAM fueling essential survival and resistance opposing therapeutic strategies aimed at disrupting bacterial metabolism. [44] SAM is utilized by pathogens to support methylation-dependent defenses, such as rRNA methylation (resistance to ribosome-inhibiting antibiotics) and DNA modification. Methionine intake into malignant transforming cells increases with the presence of bacterial pathogens increasing SAM production desensitizing tumors to radiotherapy, silencing tumor suppressors and activating oncogenes. [45]

However, SAM can be depleted, bacterial have SAM hydrolases that break down SAM and SAM can be allocated for defending against bacteriophage infection which F. *nucleatum* is particularly susceptible. [46] Bacterial hydrolase (lyases) depleting host SAM also depresses wound repair for surgery outcome. [47] Reduction of SAM at receptor-interacting serine/threonine-protein kinase 1 (RIPK1), drives apoptosis and inflammation. [48] Although, oral pathogens depletion of arginine impairs mucosal remodeling and collagen deposition necessary for healing. [49] Moreover, SAM depletion by bacterial pathogens induces cell cycle arrest in the G1 phase. activating the stress-activated kinase p38 (MAPK14), which triggers downstream signaling through MAPK-activated protein kinase-2 (MK2) and activates wound healing but also cancer cell proliferation [50] To

 doi:10.20944/preprints202603.1932.v1

summarize, presence of pathogens increases likelihood for arginine depletion, disruption of methylation, triggering of oncogenes while reducing tumor suppressor expressions resulting in less effective therapy for OSCC but maintaining B vitamin complex and depleting SAM vitamin activities may improve healing.

5. Oral Bacteria Degradation of Tobacco Carcinogens

Tobacco products are a heterogenous mixture of chemicals and other agents that can cause biologic harm when processed through the metabolism and biology of oral bacterial pathogens. Furthermore, microplastics is an emerging environmental exposure with tobacco smoke products and chemicals. PAH and TSNAs, and microplastics have an compatible affinity for gram negative bacteria surface attaching by cationic charge and/or lipophilia (**Figures 3 and 4**). Bacteria become intercellular carriers for PAHs, heavy metals, and microplastics after they attachment to oral epithelial surface. Intracellular transport of reactive chemicals-toxins, alter both microbial metabolism but also host epithelial cell metabolism, causing activation of AHR signaling. [51–55] Persistent complexes of microplastics, carcinogens, and pathogens induce membrane destabilization, apoptotic mimicry, immune dysregulation, and chronic inflammation, promoting mucosal pro-oncogenic microenvironment. [56–61] Only two studies have directly examined the microbial degradation of tobacco products in the oral environment. Tao et al. (2024) reported associations between oral bacterial and fungal communities and tobacco smoke constituents, demonstrating consequent DNA adduct formation. Similarly, Ramono et al. identified DNA damage, including double-strand breaks, in exfoliated oral epithelial cells from smokers. [62,63] Although there are increasing number of studies identifying bacteria associated with established cancers or precancerous lesions using microbiome sequencing. Our literature analysis (**Table 2A–B**) identified a distinct group of bacterial taxa that do not initially overlap with clinical lesions. We propose that these organisms represent an intermediate microbial population that survives on tobacco-derived substrates such as PAHs and N-nitrosamines. (**Tables 1.2, Figures 1 and 2**) Over time, microbiomes will change to survive anaerobic conditions (e.g., HIF-1 expression increases) and pathogenic species release of virulence factors interacting with host essential amino acids (e.g., arginine, tryptophan, methionine) influencing SAM metabolism, oxidative stress, DNA damage, and loss of epithelial homeostasis. In addition, increasing bacteria pathogen's role (e.g., DPPIV) contributes to oxidation of lipophilic metabolism amplifying diabetes, and obesity.

In addition to arginine, another essential amino acid, tryptophane and derivatives tryptamine and kynurenine results in synthesis of nicotinic acid. Nicotinic acid, nitrite, secondary and tertiary amides participate in synthesizing N-Nitrosamine such as *N*′-nitrosonornicotine (NNN) and DNA adducts and damage resulting from oxidative metabolism by CYP_{450}s (1A1). [64] Carcinogenesis can produce a high pH (metabolic alkalosis, narrowing of anion gap: alkaline saliva) as sialiolitis, and less serous and more mucoid content with elevated bicarbonate changes saliva. Salivary methyltransferase (DNMT: 1, 3A, and 3B) expressions also leads to gene promoter hypermethylation, contributing to oral dysplasia and potential malignancy as tumor suppressor expression is depressed. [65]

In addition, there is an imbalance of salivary lysozyme, peroxides, lactoferrin, immunoglobulin (sIgA) which controls pathogenic bacterial pathogenic release of proteases, metallo-peptidases, dipeptidyl-peptidases (IV), matrix-metallo-peptidases (MMP 6,9), glycation end-products and others suppressing host immune resistance. Reducing immune resistance, enhancing pathogenic survival adds to adherence to damaged stem and stemlike cells as pathogenic bacteria infiltrate through ECM (gelatinolytic activity) to reach pluripotential proliferative cells (**Figures 2–4**) [66]

Following bacterial adherence and endocytosis, extracellular and intracellular reservoirs, including multilamellar vesicles—some clathrin-coated—assist with evasion of immune recognition (**Figures 2–4**). Bacterial endopeptidases, include virulence-associated cysteine and serine proteases, matrix metalloproteinases (MMPs), dipeptidyl peptidases (DPPs), and related enzymes. These enzymes degrade extracellular matrix components and promote development of TME. Pathogen

 doi:10.20944/preprints202603.1932.v1

adherence and enzymatic activity activate membrane-associated enzymes. For example, phosphokinase signaling, induces multiple transcriptional complexes, including ETS-1, HIF-1, AHR–PAS–bHLH, NF-κB, and receptor tyrosine kinases (RTKs). [67] Transcriptional expressions from receptors cause loss of cell-cycle checkpoint control and increased genomic instability, characterized by biomolecular condensate formation and dysregulated cell–cell interactions. These factors characterize TME stresses like hypoxia, inflammation, and xenobiotic signaling, causing aberrant proliferation and survival. [68,69] We reiterate pathogen accumulation in plasma and endosomal membranes disrupts ceramide–sphingomyelinase cycling, Golgi network signaling, and lipid organization, affecting lipoprotein, glycolipid, and phospholipid sorting and transport. [70,71] Subsequently ubiquitin–proteasome activity degrades host protein as expression of aberrant proto-oncogene and oncogene also occurs. For example, removing misfolded proteins and degradation-tagged tumor suppressors (e.g., p53), while simultaneously stabilizing oncoproteins (e.g., c-Myc). [72,73] Furthermore, cytokine dysregulation (e.g., IL-6, TNF-α) further compromises cellular homeostasis, promotes DNA instability, and imposes high NAD(P)H demands characteristic on proliferating malignant cells. [74] Nuclear reorganization and biomolecular condensates also reflect disruption to RNA processing and transcriptional regulation required for effective environmental sensing and gene regulation. [75,76]

Despite these extensive pathogenic interactions, there is currently no direct evidence that oral bacterial activity alone is sufficient to induce full malignant transformation in the absence of environmental chemical carcinogens. [77] Instead, the literature supports a model in which bacterial pathogens function as critical cofactors that contribute to the initiation and promotion of oral oncogenesis in a manner that is interdependent with chemical carcinogenesis. [78–80] Oral pathogens modulate key metabolic checkpoints, associated with redox homeostasis through sulphuration and glutathione (GSH/GSSG) cycling, suppressing ROS, lipid peroxidation and ferroptosis through iron–sulfur cluster metabolism while activating superoxide dismutase, and Fenton reactions. [81] Lipid peroxidation also dysregulates energy (e.g., NADPH) utilization, increasing proliferative malignant progression in combination with chemical carcinogenic exposure. [82–84]

6. Oral bacterial Pathogens Accumulating in Pre-Cancer and OSCC Lesions

Partners of individuals with periodontal disease have a 14% to 75% higher risk of acquiring pathogenic bacteria. [85] Experience with SARS-CoV-2 shows a novel predominant microbe can affect bacterial (e.g., periodontal infection), and viral presence (e.g., Epstein Barr virus). [86,87] Presence of dental plaque, deep periodontal pockets (>3mm), and biofilm reservoir for hundreds of bacterial species, have a link to systemic diseases and cancers: Pg, Fn, Td, and others such as, Treponema denticola, and Aggregatibacter actinomycetemcomitans [88] These bacteria can disseminate throughout the body [89,90] while maintaining presence in specific lesions and anatomic locations (**Table 2**). [91]

One set of bacteria species, Prevotella species (Pre-cancers: (HL) Prevotella *histicola*, (PVL) Prevotella *salivae*; OSCC: Prevotella *nanceiensis* and (PVL-OSCC) Prevotella *shahii*) are identified in all types of lesions (**Table 2**.) and in saliva samples. [92,93] Saliva sequence identification from OSCC cases identifies: Prevotella *melaninogenica*, Prevotella *tannerae*, and Prevotella *intermedia*. Although identification of Prevotella spp. in saliva from smokers is limited. Poor survival conditions for some bacteria occur because of tobacco smoke (TS). containing over 5,000 components, including highly reactive, toxic compounds such as free radicals, ROS, and toxic reactive AGE, and glycotoxins. [94] Components in tobacco smoke damages bacterial cell surface, triggers protective mechanisms like biofilm formation and quorum sensing, induces genetic changes, and virulence factors. [95] Cigarettes also generate temperatures exceeding 600 °C, with the burning tip reaching over 800 °C-900 °C during a puff. [96] Extreme heat mixed with possible toxic accumulations of reactive compounds decreases survival of some bacteria but allowing others to thrive. Elevated temperature induces heat-shock gene (e.g., chaperonin-mitochondrion-cytosol) in host and microbes. In addition, toxic aminoglycosides act like antibiotics. [97] along with heavy metals, overwhelming bacterial

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defense mechanisms, leading to protein denaturation, membrane damage, and/or increased DNA mutation rates to aid survival, resistance to antibiotics and virulence gene mutations. Bacteriostatic compounds can be N-Nitrosamines suppressing bacteria growth, but when concentrations rapidly increase then carcinogenic activity and host cell DNA adduct and damage is likely. [98] Tobacco smoke induces hypoxic conditions enhancing survival of anaerobes such as Prevotella spp. Clinically host oral cells experience ischemia, microthrombi, coagulation abnormalities, and acid-base imbalance with poor energy utilization (NADPH). [99]

Prevotella genus bacteria release virulence factors (e.g., interapin A, papain like cysteine proteases) such as cysteine proteases and cause inflammation secreted via Type IX Secretion System (T9SS). [100] *Prevotella's* virulence factors need iron (heme) proteins to bind and they sequester host porphyrin, heme portion of RBC's hemoglobin. This process causes host immune responses (hemolytic anemia). Bacterial heme acquisition regulates ROS and synthesis of heme-oxygenase-1 (HO-1) from monocytes managing heme toxicity, providing heme to creates complex interactions during infection. [101] *Prevotella* is a gram-negative bacterium, displaying LPS/Lipid A endotoxin, inducing disorganization in lipophilic-hydrophilic host epithelial membrane components. *Prevotella* causes PRR, adherence to TLR 2,4; triggers ceramide-sphingomyelinase cycling with ubiquitination-proteosome activity, disrupting maintenance of cell homeostasis and lipid/lipoproteins-small chain fatty acid (SCFA) synthesis and functions. **[102,103]** *Prevotella* stimulates epithelial cells to produce IL-8, IL-6 and CCL20, to promote mucosal inflammatory microenvironments, acting on macrophages and B cells to induce or amplify the expression of cytokines, autoantibody, Th17, and IL-17 expression with loss of tolerance immune responses and neutrophil recruitment. **[104]** In addition there is an inhibition of C3b and C4b from release of serine protease Factor 1 (F1). Pathogenic *Prevotella* species also release proteases degrading immunoglobulins, and sialidase producing free sialic acid, increasing mitogenic amplification of LPS function, causing coagulation disorders, degradation of extracellular polysaccharides (EPS), extracellular matrix (ECM) aiding cell adherence and invasion by Prevotella and cancer cells into tissue possibly reason for high identification in pre-cancer and OSCC. Prevotella species release virulence factor outer membrane vesicles (OMV) to transport enzymes and toxins, with display of fimbriae improving adherence to epithelial membrane promoting endocytosis and release of virulence factors in epithelial cells. [105] In *Prevotella's* biofilm, quorum sensing releases, beta-lactamases inactivating antibiotics, while enhancing survival. All these activities are likely present to aid *Prevotella* species to accumulate in pre-cancers and OSCC (**Table 2**)

Pseudomonas *aeruginosa* (**Table 1**.) another gram-negative bacterium uses dioxygenases (monooxygenation or deoxygenation) to produce phthalates and hydrolases degrading PAHs. P. *aeruginosa* also produces biosurfactants increasing PAH solubility, increasing bioavailability, with degradation and induction of CYP_{450}s (e.g., 1A1) producing diol-epoxides for ligand attachment to AHR triggering environmental sensor activities. **[106]**

Different pre-cancer lesions such as homogenous leukoplakias (HL) type lesions (**Table 2**), show reversible hyperplasia identified with bacterial pathogens. **[107]** In contrast, salivary samples from OSCC, cited by three studies, show a more diverse group of bacteria. This is because saliva provides a global landscape of microbiome not specific for a specific lesion. However, OSCC includes Streptococcus anginous, Prevotella spp., and Fusobacterium spp, *periodonticum, and nucleatum.* Again, we note, smoking alters survival of bacteria, reducing diversity, especially commensal bacteria. Among smokers: *Selenomonas* ; *Synergistes* genera Fusobacterium, *Cardiobacterium*, as well as respiratory pathogens of Pseudomonas *aeruginosa* and Hemophilus *parainfluenzae* are identified. **[108]** Both P aeruginosa, and H. parainfluenza degrades PAH contributing to AHR activation, environmental sensing, and risk for OSCC. To sum up we present **Figure 3.** where we provide an overview of microbial biofilm response to environmental exposomes producing cellular interactive molecular responses.

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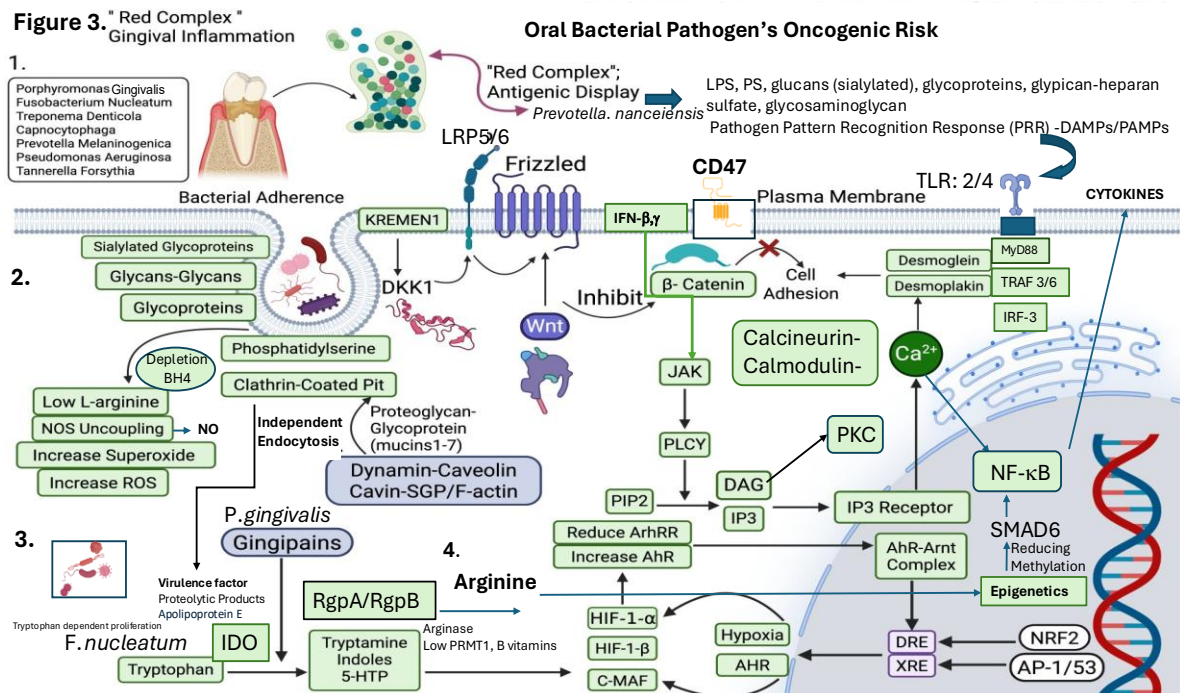

Figure 3. (**1**.) An aggregation of "red complex"-gingival inflammatory bacterial pathogens migrate from gingival biofilm to malignant transformation site. Most bacteria are gram positive but predominant virulent bacteria are gram negative, displaying *LPS, and endotoxin Lipid A* triggering lipid membrane mitogenic PRR damage associated microbial pattern (DAMP), or pathogen associated microbial pattern (PAMP) with attachment to TLR 2,4. They display *glycan-glycosaminoglycans, sialylated-glycoproteins; glypican-heparan-sulfate*, or surface display of phosphatidylserine (*PS*). Membrane PS flipping from inner to the outer surface of dying or stressed cells (apoptosis/necroptosis) alerting phagocytes for engulfment, attempting to reduce inflammation. Phagocytes recognize PS via integrin like receptors, or MER proto-oncogene, tyrosine kinase (MerTK, a RTK). Internalization of PS is a process vital for tissue homeostasis, development of immunity, cancer and triggering protease activated receptors-2 (*PAR2*) targeted by P. gingivalis and other gingival bacterial pathogens. PAR2 is a G-protein coupled receptor activated by proteases (like trypsin, tryptase), creating a "tethered ligand" that binds to the receptor, initiating intracellular inflammatory signals, for cytokines, and MMPs, affecting mucosa and ECM. Adherence to receptors triggers signals into the cytosol using adapter molecules (e.g., MYD88) transferring signals to NF-⍟B. Membrane blebbing, endocytosis multilamellar vesicle, and exposed oxidative lipophilic domains of receptors all assist with local membrane deformation and signals from transmembrane protease (TMPRSS1/2) and kringle transmembrane protein-1 (*KREMEN*) gene expressions to encode transmembrane proteins regulating wingless (*Wnt*) via *Frizzled* (FZD) receptors. Gene KREMEN encodes a high-affinity dickkopf homolog 1 (DKK1) transmembrane receptor cooperating with DKK1 to block WNT/beta-catenin and Wnt(5a) promoting differentiation of oral keratinocytes. Wnt5a and calcium activates Wnt/β-catenin signaling increasing stability of β-catenin non-dysplastic cells, enhancing β-catenin transcriptional activity and mucosal viability. Free calcium occurs as calcineurin, a phosphatase, binds to calmodulin depressing mucosal viability while conserving virulence from pathogens. Depressing calcium increases dedifferentiation, and cancer cell proliferation enhancing malignant transformation risk. (**2**) Bacterial pathogens undergo endocytosis enters oral epithelial cell and release endopeptidases: bacterial derived endopeptidases (e.g., (zinc) (Matrix) metallo-dipeptidyl-peptidases (MMPs; Subtilisin; neurophilin-1 (NSP1) metallo-peptidase (e.g., ADAM-17), cathepsins, gingipains (e.g., cysteine proteases), cooperate with PS to facilitate expression (e.g., *NOTCH*). *Notch* gene functions act as a transmembrane receptor for epidermal growth factors (EGF)-like repeats, activated by transmembrane ligands expressed on adjacent cells functioning as an oncogene reprogramming tumor microenvironment (TME). NOTCH dysregulation promotes epithelial-mesenchymal transition (EMT) and angiogenesis with cancer cell proliferation, invasion, and metastasis. Furthermore, Notch signaling contributes to maintaining stem-like properties in cancer cells, enhancing cancer invasiveness as bacterial pathogens infiltrate deeper into epithelium disrupting EMT. Signals from JAK-STATs /NFATs will result in kinase activity

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and eventually transcriptional expression by NF-kB under regulation by hypoxia inducible factor-1 (HIF-1) transcription expression under hypoxic conditions. Inflammatory signal amplifies an array of receptors such as TAM tyrosine kinase receptors (RTKs) including Tyro3, Axl, with ligands Gas6 and Protein S (PROS1) crucial to clearance of apoptotic cells (efferocytosis), immune system regulation, and tissue homeostasis. PROS1 an upregulated marker for OSCC proliferation, cell survival and migration. (**3-4.)** Pathogens release of virulence factors, cysteine proteases, gingipains (arginine specific: Rgp/Rga/lysine specific: Kgp) disrupt host cell maintenance of homeostasis altering arginine and tryptophan-tryptamine metabolism and activation of transcriptional complexes, NF-kB to synthesize cytokines and other transcriptional expressions mediating environmental sensing such as AHR-PAS-bHLH. Lysine metabolism is also influenced to include collagen cross-linking, post-translational histone modifications (e.g., methylation, acetylation) and fatty acid beta oxidation for carnitine biosynthesis. These activities complement chemical carcinogenesis from environmental exposomes and combined with persistent DNA damage site induction (DRE/XRE) producing proto-oncogenes and oncogenes expressions mediate cancer cell proliferation and with expression of E3 ubiquitin ligase further destabilize DNA promoting full malignant transformation of oral epithelial cells to establish OSCC.

In comparison to healthy microbiomes, the smoking habit and presence of pre-cancer or OSCC lesions identifies with predominant presence of gram-negative bacteria. **[109]** For example, gram-positive Streptococcus anginous, (SAG group) initially a commensal bacterium, sustains symbiosis can become pathogenic and releases DNases causing DNA instability. Like other Streptococci, proteases degrade sIgA, and synthesize metallo-dipeptidylpeptidases (DPPs) such as, dipeptidyl peptidase IV (DPP IV) inducing a diabetogenic metabolism while releasing endotoxins resulting in host loss of tolerance and IL-17 expression (**Figure 4.**). **[110]** Bacterial heterogeneity and diversity change can be a product of sample site and individualization when sampling indicating a need to have invariant markers for function and oncogenesis. **[111–124]**

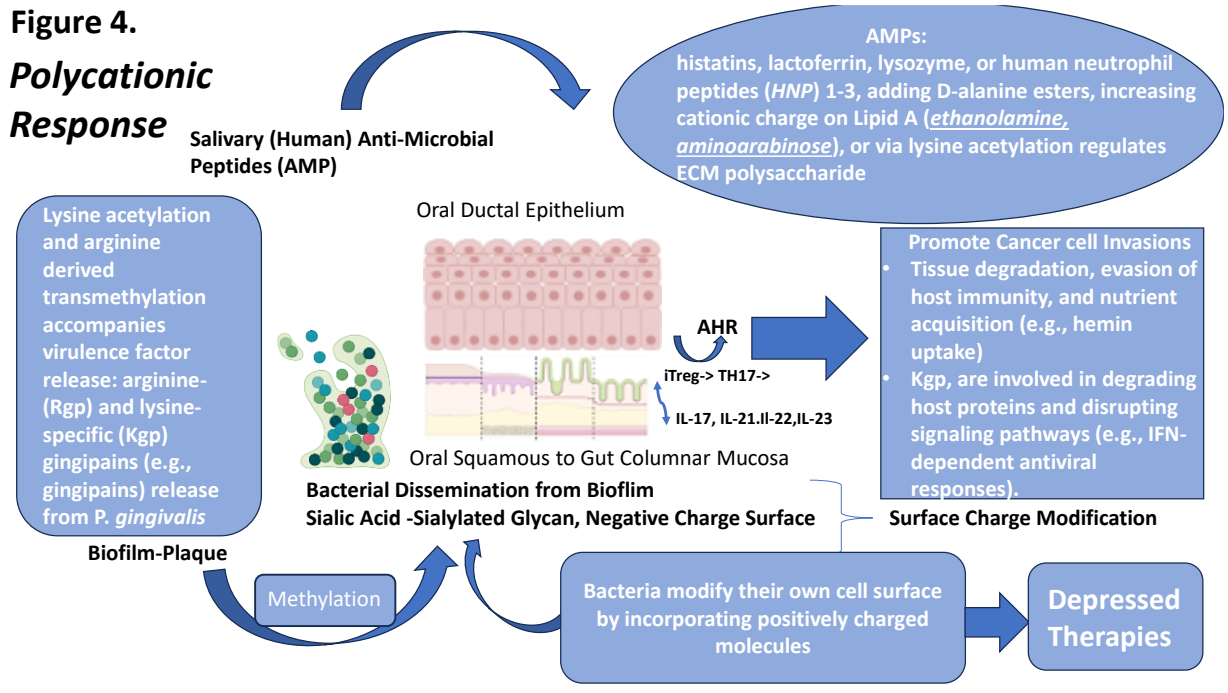

Figure 4. During this process, bacteria escape from biofilm and plaque and try to evade but salivary anti-microbial peptides (AMP): which form the *polycationic response.* Bacteria modify their own cell surface by incorporating positively charged molecules increasing survival in bioflim. This mechanism, known as surface charge modification, makes the bacterial surface less negatively charged, thereby repelling the positively charged host AMPs. [93]. AMP are composed of histatins, lactoferrin, lysozyme, or human neutrophil peptides (*HNP*) 1-3, adding D-alanine esters, increasing cationic charge on Lipid A (*ethanolamine, aminoarabinose*), or via lysine acetylation. The consequence is attachment of AMP to bacteria (e.g., P.*gingivalis* or F.*nucleatum*) with negligible effect as a virulence factor such as arginine and lysine gingipains and epigenetics factors triggering

 doi:10.20944/preprints202603.1932.v1

arginine related SAM methylation, expression of arginase-1 (ARG), arginine demethylase in contrast to salivary arginine methyltransferase to suppress p53 tumor suppressor function as virulence factor Rgp release also activates indoleamine-1 (IDO) and indoleamine synthesis related to tryptamine-tryptophan metabolism and activation of AHR-PAS-bHLH environmental sensing transcriptional function. It is through methylation guided by bacterial pathogen requirements for arginine, and methionine that silencing of tumor suppressors (hypermethylation) and expression of oncogenes (hypomethylation) results in suppression of OSCC therapies. This metabolic activity is initiated following bacteria attachments to plasma and endosomal receptors (e.g., TLR 2,4, 3) initiating signals (STATs,/NFATs) from the membrane, mediated by adapter proteins (e.g., MYD88) that induce a variety of transcriptional complexes such as NF-kB, HIF-1, and AHR-PAS-bHLH. In addition to the synthesis of cytokines, the adaptation to hypoxia conditions, which depresses energy utilization (e.g., NAD[P]H) there is also differentiation from CD4+ or CD8+: T regulatory cells which can synthesis immunosuppressive cytokines and cytotoxicity inhibitors reducing tumor surveillance and cytotoxicity. In addition, degradation of host proteins through loss of inflammatory control and induction of ischemia (e.g., heme degradation) with metabolic depletion of essential amino acids (e.g., arginine) produces a suppressed potential for efficient and optimum therapies such immunotherapy, chemotherapy, radiation, and surgery.

7. Environmental Influence on Metabolic Active Biofilm

Exposure to environmental exposomes (**Figure 1**.) causes dysbiosis and interaction with oral epithelial mucosa specifically stem and stem cells like cells.

1) Oral disease related biofilms (e.g., plaque) shift with loss of diversity (alpha, beta) and accumulation of specific species in specific lesions. (**Table 2)**.

2) Sites of gingival and mucosal inflammation, biofilm formations may develop adjacent to lesions and in response bacteria pathogens contribute to host metabolism and enzymology in sites of high-risk sites for leukoplakias (irreversible), and erythroplakia or another lesion of pre-cancer: (proliferative) verrucous leukoplakia; caused by an oral virus, human papilloma virus (HPV), at risk for oral oncogenesis and in OSCC. (**Table 2. A., B**.)

High risk sites for OSCC include *lateral border of the tongue*, *floor of mouth*, *buccal vestibule-buccal mucosa*, gingiva and *lip*. Sites are high risk because of protective barrier loss and a dampening of epithelial homeostasis. A less protective barrier is found because of insufficient resilience of cytokeratin protection (e.g., low molecular cytokeratin vs less high molecular weight cytokeratins) with reduced repair because of continual mechanical stress and increasing incidence for irreversible basal dysplastic cells producing lesions with loss of desmosome intercellular bridge attachment. Specifically, reduced is desmoplakin and/or interconnection to intermediate filament networks reducing sheet-like structure to reinforce the entire tissue to withstand mechanical stress. We noted above high levels of cysteine and serine proteases, MPPs, and DPPs, released by bacterial pathogens located in adjacent biofilm, degrading cadherins: desmogleins, desmocolins transmembrane anchors, plakoglobins and plakophilins damaging linking to cadherins and other related proteins reducing intercellular communication responding to TME. [125,126] Loss of cellular and tissue integrity and reduced tumor immune surveillance and cytotoxicity enhance opportunity for infiltrative pathogens and virulence factors. Pathogens adhere and enter oral basal or basal-stem cell like cells to assist with clonal expansion. Cells in clones exhibit increasing damage to checkpoint control regulation as they undergo malignant transformation. Oral bacteria pathogens degradation of PAH already discussed (**Table 1**.), form diol-epoxides and DNA adduct with endogenous (e.g., nitrosation, N-Nitrosamines) adducts formations also contributing. In addition, habitual sources of carcinogens add TSNA: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). Degradation by metabolic activation from CYP450 1A1, intermediates forming methylate and pyridyloxobutylate DNA adducts also appear to show enhanced DNA instability. [127]

3) **Oral Alcohol's Role:** In addition to tobacco products there are additional exposures to environmental pollutants, with alcohol metabolism studies showing that 70% or more of tobacco smokers also drink alcohol. [128] Persistent of reactive agents such as alcohols results in dysbiosis and basal cell-stem cell malignant transformation (**Figure 2.)** Alcohol is metabolized using alcohol

 doi:10.20944/preprints202603.1932.v1

dehydrogenase (ADH1,2) creating a possible carcinogen, acetaldehyde. **[129]** This metabolism can occur in oral bacteria, oral epithelial cells **[130]** and in non-oral cells especially. liver. Through gene expressions of aldehyde dehydrogenase (ALDH) there is a control of acetaldehyde exposures. Using the OncoDB database (ANOVA p-value:1.4e-02) (https://oncodb.org/) we note significant probability for over-expression of ***ALDH1L2*** in oral squamous cancer compared to normal. False discovery rate (FDR): p-value:1.4e-11 ([log2FC: 1.69]) was significant for probable expression. (https://oncodb.org/) ALDH1L2, aldehyde dehydrogenase isoenzyme, (*ALDH2*2* gene variant)expression correlates with development and progression of oral cancer, and some leukoplakias (irreversible type). ALDH1L2 is also a marker for cancer stem cells (CSCs), mitochondrional dysfunction with loss energy utilization; associated with poor prognosis, chemoresistance in OSCC, and protection from acetaldehyde. [79] Furthermore a form of ALDH is available for some oral bacteria to produce acetaldehyde suggesting oral bacterial oncogenic activity not often considered.

Exposure to alcohol and then acetaldehyde generates genotoxicity reactions to form a variety of different types of DNA adducts. For example, N2-ethylidene-deoxyguanosine (N2-ethylidene-dG), reacting with the guanine base in DNA, a reaction critical in alcohol-related cancer, as these adducts can block DNA synthesis leading to mutations. **[131]** Acetaldehyde also forms other adducts, including N^6-ethyldeoxyadenosine (N^6-ethyl-dA) and N^4-ethyldeoxycytidine. [81] Alcohol also increases AHR transcriptional environmental sensing inducing autophagy and aberrant lipid metabolism in stem cells, leading to mitochondrial dysfunction, lipid accumulations in oral tissues such as salivary glands. Resulting is xerostomia with mucins and mucoid saliva (**Figure 4**.). [132] Additional lipid formations include ceramide, lipid droplets (LDs), which primarily accumulate triglycerides (TAGs) and cholesteryl esters, and identify with alcoholic liver disease (ALD) but sometimes with AHR as a useful marker for OSCC linked to ALD. **[133]** Concentrations of alcohol will also pharmacologically affect biomolecular condensates, chromatin and histone modifications to influence peptide substrate availability for tyrosine (e.g., RTKs), altering related phosphorylation epigenetics, although alcohol is not a ligand for RTK. **[134]** Expressing ALDH can culminate into forming acetate, reducing the risk for mutation but with a deficiency of ALDH2 in Asian populations indicates a slow breakdown of acetaldehyde and tendency for accumulation in oral and non-oral epithelial cells. [135]

To sum up, oral cavity metabolic activity drives endogenous carcinogen synthesis: forming adducts while oral bacteria express ALDH, creating acetaldehyde adducts and PAH derived adducts. PAH and alcohol via bacterial metabolism gene transcription also triggers tryptophan-tryptamine synthesis for AHR transcription and environmental sensing enhancing oxidative stress, DNA damage and DNA mutations.

(4) Viral Influence on oral bacteria: Oral bacteria pathogens are dependent on viral genetic information modifying alcohol and acetaldehyde metabolism provided by bacteriophage and transposons or casposons. a mobile genetic element, acting like bacteriophage in bacteria like P. *gingivalis*, F. *nulceatum* and Archaea ancestors. [136] In a specialized CRISPR-Cas adaptive immunity system, "self-replicating transposons" copy and move within a genome, as a "casposase" enzyme influences ALDH. **[137]** Bacterial pathogen use a similar transposons process to enhance metabolic activity for alcohol that uses metal ion (e.g., Sn++, Cr++, Cu++, Ni++, Fe++) binding in presence of alcohol producing acetaldehyde to enhance risk for DNA damage in bacteria or in host epithelial cells.**[138]** Repair occurs by interstrand crosslinks resulting in increased mutation frequency and an altered mutational spectrum or replication fork convergence not involving DNA incisions—instead acetaldehyde crosslink itself is broken. [139]

Further we note (**Figures 2.,4**.) clearance and dissemination of bacterial pathogens may become overshadowed by environmental exposomes driving chemical carcinogenesis

 doi:10.20944/preprints202603.1932.v1

8. Lipophilic Oncogenic Gram-Negative Oral Bacteria and Environmental Carcinogens

We reviewed several lipophilic chemical carcinogens compatibilities with gram negative bacteria (e.g., Pg, Fn) resulting in epithelial cell's metabolism and membrane disorganizational changes. Bacterial pathogenic adherence to oral epithelium accompanies SCFAs (e.g., butyrate, propionate, and acetate) cell responses. [140] SCFAs act as energy substrates inhibiting HDAC, activating G protein coupled receptors (GPCRs) while signaling differentiation for CD4+/CD8+ to T_{reg}s, with AHR oversight synthesizing immunosuppressor cytokines (IL-10, TGF-b). [141] When cells are stressed SCFA influences sphingomyelinase (aSMase) hydrolyzing sphingomyelin to ceramide. [142] Breaking down ceramide as a barrier preventing pathogen entry and signaling in the cell and coordinating chronic inflammatory responses. For periodontal disease, apoptosis, clearance of pathogen [143] enhancing HNSCC poor prognosis. Futhermore, ceramide, C16-ceramide elevation promotes cell survival, migration, and resistance to therapy. [144] *Pg*, also produces specialized dihydroceramides (PEDHC) inducing intracellular ceramide in cancer cells, increasing survival. [145] Pg and Fn use SCFA to assist in expression of granzyme, which results in perforin release from granules in T lymphocytes depressing host immunity, as their LPS activates NF-κB, transcription and cytokine expressions (TNF-α, IL-6). [146] In turn, periodontal pathogens cause adipokine production, enhancing expression of pro-inflammatory adipokines: leptin, resistin, visfatin, IL-6, and MCP-1, but depressing adiponectin (anti-inflammatory) enhancing gingival inflammation, and diabetes (e.g., DPPIV/CD26). [147] Thus, increasing presence of malignant transformed epithelial cells and inflammatory signals (e.g., Fenton reaction products, NOX2-4, iNOS genes) in adipocytes and in oral and non-oral epithelial cells. [148,149]

Pg infection also increases expression of the fatty acid transporter CD36 and the transcription factor PPARγ, inducing lipids with higher triglyceride and cholesterol to accumulate in salivary gland, and adipose tissues reducing salivary functions and lowering glycolysis activities via DPPIV expression inducing diabetic risk. [150] In addition, gram negative bacteria, displays LPS triggering TLR: 2-4/MyD88 and NFκB expressions enhancing PS ('Eat Me") expressions for phagocytes in contrast to a CD47, "Don't eat Me". Oral epithelial lipophilic characteristics are also targets for adherence through lipoprotein, PS like domains on T cell immunoglobulin like mucin receptors (TIM). TIMs are important for antigen recognition, cell-to-cell interactions, and direct membrane signaling into host epithelial cell to guide cell organization and transcriptions. Pg also produces unique bacterial sphingolipids and serine dipeptide lipids as virulence factors OMV, multilamellar lipophilic vesicles aid evasion of host immune defenses [151] and assist in lipophilic compatible affinity between bacterial surfaces and PAHs, N-Nitrosamines, aldehydes, alcohols, and alkaloids, and microplastics. These interactions increasing potential aggregations of bacteria, disorganizing epithelial membrane cycling creating instability with loss of nuclear membrane integrity and cytosol interactions.

Butyrate is a SCFA anti-inflammatory agent but association with soluble phospholipids: choline, and phosphatidylcholine formations can affect oxidation, and as a HDAC inhibitor, increasing SCFA and MMPs degrading of epithelial-mesenchymal transition (EMT) enhances invasion of oral squamous cell carcinoma. In this case, inhibition of cancer cell growth could also come from induction of adenosine-mono-phosphate kinase (AMPK), an energy sensor suppressor and autophagy inducer in oral carcinoma by inhibiting anabolic activity and causing cell cycle arrest in cancer cells.

Pg influences TMA-TMAO pathway and increase trimethylamine oxide (TMAO). TMAO promotes oral cancer progression through inflammation, oxidative stress, and DNA damage.**[152]** High levels of TMAO occur in OSCC suggesting a diet of choline and amino acid, L-carnitine and TMAO can become elevated in periodontal disease. Pg and other pathogens also indirectly influence L-carnitine, a quaternary ammonium compound, with amino acid derivatives affecting lysine virulence factor Kgp activity and methionine affecting arginine-SAM metabolism. Transporting long-chain fatty acids (LCFA) into cell mitochondria also influences energy production and interaction with cell membrane phospholipids signals for DNA damage repair and protein misfolding. **[153]**

 doi:10.20944/preprints202603.1932.v1

Furthermore, PAHs and TMAO form complexes on surfaces of pathogens such as, Pg and Fn encouraging their endocytosis into oral epithelium. However, anti-inflammatory and inhibitory activity for SCFA may occur through histone deacetylation (HDAC) which inhibits GPR41-mediated Extracellular Signal-Regulated Kinase (ERK), promoting cancer growth.

Taken together oral and gut bacterial pathogens are engaged in mediating lipid metabolism which may or may not promote loss of oral epithelial homeostasis,

9. Conclusions

Oral bacterial oncogenesis alone is unlikely to independently drive complete malignant transformation of the oral epithelium. Rather, the mechanisms indicate bacterial pathogens transmitted between people can act in parallel with endogenous induction of carcinogens and DNA adducts establish metabolic (e.g., tryptophan, arginine, methionine) and enzymology (e.g.., endopeptidases) imbalances functioning as initiators and promoters of chemical carcinogenesis. Antimetabolite, alkylating, and anti-mitotic activities generated from bacterial interaction with host metabolism can suppress therapies for oral carcinoma. Bacterial pathogens release a variety of virulence factors that disrupt hydrophilic–lipophilic organization of epithelial cell membranes, thereby compromising membrane integrity and DNA stability and sustaining chemical carcinogenesis. Virulence factors also assist with loss of tumor immune surveillance and reduced cytotoxic activity of natural killer (NK) cells and T lymphocytes emphasizing a need to assess before using immunotherapy. Concurrently, pathogen-induced host protein degradation impairs NADPH-dependent energy metabolism and promotes aberrant regulation of DNA repair mechanisms, proto-oncogene, and oncogene expression. Environmental exposomes drives predominance of pathogenic species under dysbiosis conditions, contributing to both endogenous and exogenous accumulation of electrophilic reactive molecules, substrates for key enzymatic systems, including epoxide hydrolases and alcohol/aldehyde dehydrogenases (ADH/ALDH), generating carcinogenic intermediates such as PAH-derived diol-epoxides, tobacco-specific nitrosamine (TSNA) derivatives, and acetaldehyde, all of which promote DNA adduct formation, genomic instability, and mutagenesis.

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Abbreviations

The following abbreviations are used in this manuscript:

N-Nitrosamines (TSNA)
N′-nitrosonornicotine (NNN)
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)
Poly-aromatic hydrocarbons (PAHs)
aryl-hydrocarbon receptor (AHR)
Oral squamous cells carcinoma (OSCC)
Lipopolysaccharide (LPS)

 doi:10.20944/preprints202603.1932.v1

Trimethylamine oxide (TMAO)
Tumor microenvironment (TME)
Activator protein-1 (AP-1)
Tyrosine kinase receptors (RTKs)
Protein C-ets-1, Proto-Oncogene 1, Transcription Factor (ETS-1)
Hypoxia inducible factor-1(HIF-1)
Nuclear Factor kappa B(NF-kB)
T regulatory cells (Tregs)
Per-Arnt-Sim (PAS)
Basic Helix loop helix (bHLH)
Indoleamine 2,3-dioxygenase (IDO)
Transforming growth factor beta (TGF-b)
Programmed Cell Death 1(PD-1)
Lymphocyte-activation gene 3 (LGA-3,CD223)
Cytotoxic T-Lymphocyte Associated Protein 4(CTLA-4)
Phosphatase inhibitors (PP1)
Rho-kinase (ROCK)
Metallo-matrix peptidases(MMPs)
Metallo-matrix dipeptidyl-peptidases (DPP)
Extracellular matrix (ECM)
Epidermal growth factor receptor (EGFR)
Phosphatase and Tensin Homolog (PTEN)
Mammalian target of rapamycin (mTor)
S-adenosyl-methionine (SAM)
Cytochrome P450 (CYP450)
Aldo-keto reductases (AKR)
Tobacco specific nitrosamines (TSNA)
Anti-microbial peptides (AMP)
Pyridyloxobutyl (POB)
Phosphoditylinositol-3-kinase (PI3K)
Protein Kinase B (Akt)
Protein-38, mitogen-activated protein kinase (p38MAPK)
Extracellular matrices (ECM)
Toll-like receptors (TLR)
Phosphatidylserine (PS)
Methyltransferase (DNMT)
Secretory- Immunoglobulin IgA (sIgA)
Porphyromonas gingivalis (Pg)
Fusobacterium nucleatum (Fn)
Treponema denticola (Td)
N7-Methylguanine (N7-MeG)
N3-methyladenine (N3-MeA)
5-methyltetrahydrofolate (5-MTHF).
Radiation therapy (RT)
Stress-activated kinase p38 (MAPK14)
MAPK-activated protein kinase-2 (MK2)
Alcohol dehydrogenase (ADH)
Aldehyde dehydrogenase (ALDH)
N6-ethyldeoxyadenosine (N6-ethyl-dA) and N4-ethyldeoxycytidine
Short chair fatty acids (SCFA)
G protein coupled receptors (GPCRs)

 doi:10.20944/preprints202603.1932.v1

Histone deacetylase (HDAC)
Sphingomyelinase (aSMase)
Dihydroceramides (PEDHC)
T cell immunoglobulin like mucin receptor (TIM)
Outer membrane vesicle (OMV)
Adenosine-mono-phosphate kinase (AMPK)
Epithelial-mesenchymal transition (EMT)
Trimethylamine oxide (TMAO)
Trimethylamine (TMA)
Long-chain fatty acids (LCFA)
Extracellular Signal-Regulated Kinase (ERK)

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