Review

Chronic Inflammation and Carcinogenesis - Emerging Role of Chronic Inflammatory Periodontal Disease

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ABSTRACT

With exponential increase in the number of cases of cancers worldwide in recent past, it is imperative to enhance our understanding about the etiologic and risk factors associated with this seriously morbid condition. Increasing attention has been focussed on chronic infections and inflammatory diseases, implicating a role in carcinogenesis, particularly in developing countries. Periodontal disease is a bacterially induced chronic inflammatory process that affects tooth supporting connective tissue and alveolar bone in the oral cavity, potentially leading to tooth loss. The concept of these diseases as localized entities affecting only the teeth and supporting apparatus has been revised lately, in the light of mounting evidence of periodontal infection's influence on chronic inflammatory disease states. Periodontal disease has been linked to several systemic conditions like cardiovascular diseases, diabetes mellitus, adverse pregnancy outcomes, obesity and cancers, yet underlying mechanisms are still elucidating. The focus of this review article will be an in depth discussion of the role of chronic inflammation, particularly chronic periodontal inflammation in causation or association of human cancers and discussion of possible biological mechanisms involved.

KEYWORDS : Cancer; Periodontal disease; Inflammation; Carcinogenesis

1.INTRODUCTION

World Health Organization anticipates approximately 70% increase over the next two decades, from 14 million in 2012 to 25 million new cancer cases a year worldwide. The latest World Cancer Report emphasizes on the prevention of emergence of new cases, as cancer treatments as well as morbidity and mortality associated with disease is quite a significant global psychological and economic burden to the affected nations. It seems to be difficult to handle issue even for developed

countries, whereas low income developing nations are almost inadequately equipped for the rising burden. Most of cancers in low income nations fall in two major categories-1) triggered by infections and 2) associated with more affluent behavioural factors "with increasing use of tobacco, consumption of alcohol and highly processed foods and lack of physical activity"

23.6% of overall deaths due to cancer are caused by lung cancer, which is the most commonly diagnosed among men (16.7% of cases). In females, breast cancer is the most common diagnosis and is responsible for 14.7% of deaths. Bowel, prostate and stomach cancer are the other most common diagnoses (1). Head and neck squamous cell carcinoma (HNSCC) represents the fifth most frequent cancer worldwide (2-3). Approx.90% of cancers related to mouth, are oral squamous cell carcinoma (OSCC) making it the eighth most common human malignancies (4). Notably, oral cancer was recently included among the World Health Organization's (WHO) priorities for action (5,6).

Current knowledge about the major etiologic and risk factors associated with cancers is limited to smoking cigarettes, cigars or pipes ,chewing tobacco or betel quid (paan), alcohol, infections such as *H.pylori* and Human papilloma virus (HPV) infection, diet, sunlight, exposure to chemicals, pre-cancerous conditions and family history (7). In spite of exponential advances in medicine and technology continuously leading to a greater understanding about many human diseases, no significant decrease in incidence of malignancies and /or their morbidity and mortality or improvement in survival rate has been accomplished in case of many kinds of human cancers. Contemporary situations essentially call for devising newer ways to fight back cancer with strategies as reducing risk for cancers, early detection and highly effective therapeutic modalities. This requires an in-sight in to the different mechanisms contributing to carcinogenesis. The prognosis and survival of these patients definitely is impacted by the kind of etiologic and risk factors associated with the clinical situation as patients with HPV-positive oropharyngeal carcinomas had a significant better prognosis than the HPV negative collective (8,9).This finding might point at subtypes of infection induced carcinomas with different clinical behaviours, thus, stressing the need of further characterization of biologic processes (10). Recent reports have linked periodontal disease with increased risk of cancers at different sites in body, including oral cancers.

The focus of this review article will be an in depth discussion of the role of chronic inflammation, particularly chronic periodontal inflammation in causation or association of human cancers and discussion of possible biological mechanisms involved.

2.CHRONIC INFLAMMATION AND CARCINOGENESIS - GENERAL ASPECTS

Inflammation caused by infections has been suggested to be one of the most important and preventable causes of cancers, in general. The German Pathologist Virchow is credited with suggesting the causal link between inflammation and cancer in the 19th century (11). Chronic inflammation associated with microbial infections (*Helicobacter pylori*), autoimmune diseases (inflammatory bowel disease), inflammatory conditions of unknown origin (prostatitis) and smoking are well documented to increase the risk of certain cancers (12). Tumors are frequently surrounded by an inflammatory microenvironment rich in inflammatory cytokines, growth factors, and chemokines, which actively promote malignant cellular growth. These factors are produced by the tumor itself and its surrounding tissue and contribute to the progression towards malignancy. Epidemiological studies have attributed up to 25% of cancer deaths worldwide to chronic inflammation (3,11,13). Cancer related inflammation can fall into one of two categories, either as precancerous inflammation lesion or Inflammation that is present in almost all cancer tissues including those that have no precancerous inflammation lesions. The biological mechanism of the

association between chronic infection/ inflammation and cancer has been described quite variably and extensively (14-17).

Inflammation and carcinogenesis can be related in two possible ways- 1) extrinsic mechanism in which a persistent constant inflammatory load can enhance susceptibility for cancer initiation e.g inflammatory bowel disease 2) intrinsic mechanism, where acquired genetic alterations can incite tumour development. Inactivation of tumour suppressor genes and the acquisition of oncogenic mutations through a variety genetic and epigenetic mechanisms have been documented to be responsible for such cancer triggering mechanisms (18). Due to the similarity of aberrant DNA methylation changes (Hypermethylation of tumor suppressor genes) in cancer and aging, Some of the authors have speculated that aging is epigenetically predisposed to cancer by altering the DNA methylation profile in cells, and cancer development perpetuates those disregulated methylation state (19,20).

Molecular mechanisms - Tumor-infiltrating leucocytes as well as cytokine related signaling pathways are critical components in the development of the inflammatory tumor microenvironment. e.g peroxynitrite, an inflammatory metabolite acts as a direct mutagenic agent (21,22). Persistent inflammatory state maintains and promotes cancer progression via tumor tissue remodeling, angiogenesis, metastasis and the suppression of the innate anticancer immune response to reach full malignancy (23).

Chronic inflammation leads to cumulative genetic and epigenetic damage - Oxidizing products generated in chronic inflammation can induce the formation and accumulation of mutagenic, toxic, and/or genome-destabilizing DNA lesions (24-30). Neutrophils, the key cells in inflammatory response are the major source of reactive oxygen species, and can also inhibit DNA base-excision repair (31,32). IL-10, an important anti-inflammatory cytokine, can suppress the activity of the DNA damage response. In, a genetic IL-10 knock out mice model of inflammatory bowel disease, the frequency of DNA mutations in colon tissue is 4-5 times higher than in wild type mice, in the absence of exogenous carcinogen (33). Reactive oxygen species can induce epigenetic changes also in the form of aberrant DNA methylation. In a mouse model of intestinal inflammation and cancer, not only is inflammation associated with increased global aberrant DNA methylation, but more than 70% of aberrantly methylated genes were Polycomb complex genes which are the major target genes (34). Inflammation caused by bacterial infection e.g *H. pylori* has been shown to be correlated with aberrant DNA methylation in gastric epithelial cells (35).

Aberrant oncogenic signaling can induce inflammation- Maintainance of malignancy is a vital phenomenon for cancer perpetuation and is mediated by activated oncogenic signaling pathways in chronic inflammation. In human papillary thyroid carcinoma, activation of the RET oncogene by chromosome rearrangement is sufficient to trigger transformation of a thyrocyte to a carcinomatous cell (36). RET-activated inflammatory proteins (colony-stimulating factors (CSFs), interleukin 1β (IL-1β), cyclooxygenase 2 (COX2), CC-chemokine ligand 2 (CCL2) and CCL20, IL-8 or CXC-chemokine ligand 8 (CXCL8 CXC-chemokine receptor 4 (CXCR4), extracellular-matrix-degrading enzymes, and lymphocyte selectin (L-selectin) were found in tumour biopsies. Primary tumors from patients with lymph-node metastasis were observed to harbour higher levels of these inflammatory proteins than in primary tumours without lymph-node metastasis. Association of higher activity of the inflammatory pathway with thyroid carcinoma metastasis was highlighted through such observations. Similar findings were reported in case of pancreatic intra-epithelial neoplasia and invasive ductal carcinoma in a mouse model pointing towards the aberrant Ras-Raf signaling pathway cooperating with chronic inflammation and inducing cancer in mutated rats (37).

Another important regulator of tumour initiation and progression, NFκB is found to be related to both precancerous inflammation as well as cancer associated inflammation.

Expression of a multitude of inflammatory cytokines, adhesion molecules, enzymes in the prostaglandin-synthesis pathway (such as COX2), inducible nitric oxide synthase (iNOS) angiogenic factors and anti-apoptotic genes (such as Bcl-2) is mediated by NFκB pathway (38).

Myconcogene activation responsible for tumour angiogenesis, metastasis and maintenance of tumour specific extracellular micro-environment, is known to be regulated by cytokines, chemokines, and recruited mast cells associated with chronic inflammation (32). Tumour suppressor genes PTEN, p16, p53 (24,39) and VHL have also been implicated in the induction of inflammatory mediators that may contribute to tumour progression (40).Transcription factors like STAT3 - TGFβ are constitutively activated in tumour cells and are involved in oncogenesis and inhibition of apoptosis. The activation of STAT3 in tumour cells has also been implicated in immune evasion via inhibition of dendritic cell maturation and the subsequent immune response (41,42).

3.PERIODONTAL INFLAMMATION - PRESPECTIVES IN CARCINOGENESIS

Approximately 15-20% of human cancers have been estimated to be associated with inflammations accompanying microbial infections (43). Such infections and inflammations linked with malignancies , are typically chronic in nature and usually observed in high prevalence in populations (44). Thus, constituting quite a significant proportion, but fortunately preventable cause of carcinogenesis. Periodontal disease, is a polymicrobial immune-inflammatory affliction characterized by the destruction of supporting structures of the teeth, including gingiva, periodontal ligament, cementum and alveolar bone, eventually leading to loss of teeth. All forms of inflammatory periodontal disease are associated with chronic inflammation; the nature of the chronicity has not been established (45,46). The disease extent and severity is dependent upon an interplay of a multitude of genetic, epigenetic, environmental factors, which determine the host immune responses towards the dysbiotic periodontal microflora subverting the host defense mechanisms lead to chronic periodontitis (47-51).

Chronic periodontal disease serves as a persistent focus of inflammatory mediators and microbial products that can disseminate in to systemic circulation and can affect organs distantly situated from oral cavity. Many such associations have been recognized and documented with robust evidence e.g cardiovascular diseases, adverse pregnancy outcomes, rheumatoid arthritis, diabetes, and pulmonary diseases (52-56).

There is mounting documentation of associations between the prevalence of periodontal disease and carcinogenesis risk in different tissues, most notably in the mouth, upper gastrointestinal system, lung, and pancreas in recent literature, underpinned by immune-inflammatory mechanisms common to both entities (57-67). Moreover, there are a variety of mechanisms ,in addition to inflammation which have been considered as contributing towards the pathogenesis of cancers such as genotoxicity, molecular mimicry and production of metabolic carcinogens by microbes residing in periodontal pockets and/or oral cavity in general (68). The severity of cancerous lesion has also been linked to periodontitis and vice-versa**,** as a study of base-of- tongue cancers indicated that patients with HPV-positive tumors had greater bone loss than those with HPV-negative lesions (69), with the authors concluding that carcinogenic lesions were more likely to be poorly differentiated in periodontitis patients compared to patients without periodontitis. Chronic exposure to microbial and host-derived products as in case of chronic periodontal disease can likely modify the oral microenvironment and possibly distant tissues,and when coupled with the presence of other risk factors of malignancy such as alcoholism, smoking etc, produces accumulative

effect leading towards enhanced suscepitibility for carcinogenesis (70).

Carcinomas of the gingiva are a unique subset of Oral squamous cell carcinoma (OSCC), constituting approximately 10% of OSCCs and can mimic a multitude of oral lesions especially those of inflammatory origin with benign features e.g gingival epulis, abcesses and chronic periodontal disease (71). Many case reports documenting gingival squamous cell carcinoma mimicking to severe localized periodontal disease showing similar symptoms of swelling, bleeding, tooth mobility, deep periodontal pockets, and bone destruction have been reported ,emphasizing a closer clinical examination and early detection of the lesion for early management (72-75). Rather, cases of other types of cancers mistaken for periodontal disease such as metastatic pancreatic cancer and osteogenic sarcoma have also been reported in literature (76).

A brief summary of evidence supportive to the association of periodontal disease and carcinogenesis is provided in table 1 (77-83). An extensive analysis of association and cancers of different tissues and organs is beyond the scope of the current paper. The readers are referred to go through excellent reviews published in this area (56,63,65,66). Recent research aims to decipher the underlying mechanisms for association of chronic periodontitis and carcinogenesis focussing on direct toxic effects of the oral microbiome and associated by products and /or through the indirect effect of chronic oral inflammation and /or a combination of multiple mechanisms, discussed in the subsequent sections.

3.1-ROLE OF PERIODONTAL MICROFLORA IN CARCINOGENESIS

3.1.1- Microbial infections and cancers (General aspects)

The concept of microbes associated with the carcinogenesis is not new, as the association of Helicobacter pylori infection with gastric adenocarcinoma , spawned an exploration for other cancer-infectious disease associations. Helicobacter pylori is the best *known* bacterium causally linked with cancer leading its categorization as a WHO class I carcinogen (84-87). According to IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 1994 majority of cancers induced by Helicobacter pylori infections is related to the inflammation caused by bacterium (87,88), Infections may alter the tumor microenvironment by inducing the expression of cytokines involved in cell proliferation, and migration. these mechanisms have been documented in many investigations, e.g in colorectal cancer due to Fusobacterium spp (89-94**),** and in hepatocellular carcinoma due to HBV (95) and EBV (96,97). Rather, recently the role of commensal microbiota has also been highlighted in inflammation-induced cancer (68,98,99). Poor oral hygiene has also been documented as an independent risk factor for development of oral malignancy, raising the possibility that diverse microbial species(bacteria, viruses and fungi) present in the oral cavity may be of importance in the in the genesis of cancer (56,100-102).

3.1.2- Diversity of microbiota associated with oral carcinogenesis

In a study of bacterial species associated with OSCC, Nagy and coworkers reported a significantly higher number of anaerobic periodontal bacteria associated with malignant lesions compared to normal mucosa, including Prevotella and Porphyromonas species (103). Another study revealed an increased levels of bacterial species including Prevotella, Porphyromonas associated with SCC, and found the levels of atleast three salivary bacterial species predictive of around 80% of SCCs (104).

A significantly increased abundance of both aerobic and anaerobic bacteria with increases in Veillonella, Fusobacterium, Prevotella, Porphyromonas, Actinomyces , Clostridium , Haemophilus, Enterobacteriaceae and Streptococcus species have been revealed in OSCC by using culture-dependent assays. Approximately 30% of cancers were

Table 1. Epidemiologic evidence supportive for the role of periodontal disease to carcinogenesis

Study Design	No. of subjects	Findings	Ref
Retrospective analysis	11,328	Association between periodontitis and various types of cancer. Strongest association with lung cancer	77
Cross-sectional analysis	475	Association of tooth loss with pancreatic cancer, but failed to establish the relation with the microbial seropositivity.	78
Case-control study (between June 15, 1999, and November 17, 2005)	NA	Each millimetre of alveolar bone loss was associated with a 5.23-fold increase in the risk of tongue cancer (odds ratio, 5.23; 95% confidence interval, 2.64 - 10.35).	61
Prospective cohort study	51,529	Men with history of periodontal disease had a 64% increased risk of pancreatic cancer than men with no history of it.	63
Case-control study	843	Significant association between two markers of poor oral hygiene (larger number DMFT and lack of poor oral hygiene)	79
Case control study	473	Each milli meter of alveolar bone loss was associated with more than a four-fold increased risk of head and neck squamous cell carcinoma	69
Linkage analysis in Swedish twins.	15,333	In the co-twin analysis, dizygotic twins with baseline periodontal disease showed 50% increase in the total cancer risk wheras in monozygotics,was markedly attenuated.	80
Population-based study of oral hygiene and head and neck squamous cell carcinoma .	NA	Periodontal disease was associated with a slightly elevated risk of HNSCC (OR = 1.09, 95 % CI: 1.02, 1.16).	62
Systemic review PubMed articles from1995 to 2010	NA	Nine out of ten case–control studies reported a significant increase in the risk of oral cancer in patients with periodontitis and one with no significant association.	83
Meta analysis utilizing random-effect model	NA	Significant association of periodontal disease with oral cancer [OR = 3.53, 95 % CI (1.52-8.23); P = 0.003]. showing increased susceptibility to oral cancer.	58

documented to harbor Candida albicans, but not at control sites (103). The association of Candida with the progression of the epithelial dysplasia in oral mucosa; i.e. oral carcinogenesis was first reported by Cawson and Williamson in 1969(68).

With current advances in microbiological techniques, recently the oral microbiome in oral squamous cell carcinomas has been studied using culture-independent assays also. Using a 16s rRNA assay an investigation of oral tongue/floor of mouth cancers showed

Streptococcus intermedius was present in 70% of both cancer and normal tissues. Streptococcus sp. oral taxon 058, Peptostreptococcus stomatis, Streptococcus salivarius, Streptococcus gordonii, Gemella haemolysans, Gemella morbillorum, Johnsonella ignava and Streptococcus parasanguinis were highly associated with the cancers and Granulicatella adiacens was prevalent the normal tissue (105). Another cohort investigation comparing oral cancers and premalignant oral lesions matched with normal contralateral tissue sites from the same patient revealed the abundance of the phyla Firmicutes (especially Streptococcus) in cancer samples and significantly decreased Actinobacteria (especially Rothia) relative to contralateral normal samples. Significant decreases in abundance of these phyla were observed for pre-cancers, but not when comparing samples from contralateral sites (tongue and floor of mouth) from healthy individuals (106). Immunohistochemistry studies in gingival carcinomas with *P. gingivalis* antibodies revealed higher levels of detection and intensity of staining in cancerous tissues as compared with healthy gingiva (107).

To put the viruses in perspective, human papillomaviruses HPV-6, -11, -16, -18, -31, -33, and -42 have been isolated from the oral cavity. HPV-16 and HPV-18 and others are regarded as carcinogenic and most common virus types identified in oral carcinoma (108-113).More recent studies have indicated that HPV may be more closely related to particular subsets of disease, specifically oropharyngeal and tonsillar carcinomas, similar to their role in cervical cancer (56,114-117). Herpes simplex viruses (HSV) nucleic acids have been found in lip cancer (118), antibody levels to HSV-1 and -2 are higher in oral cancer patients when compared with controls, and HSV seropositivity together with smoking has been associated with increased cancer risk (109). Epstein-Barr virus has also been implicated in oral cancer but the evidence thus far is controversial (113). However, it has been estimated that at least six human viruses, EBV, Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), HPV, Human T-Cell Lymphotropic Virus (HTLV-1) And Kaposi's Associated Sarcoma Virus (KSHV) Contribute to 10-15% of the Cancers Worldwide (119). It is well documented that there is much higher incidence of oral malignancies in HIV positive patients/AIDS patients and all these viruses have been associated with oral cavity in these patients.

3.1.3-Plausible mechanisms linking periodontal microflora with carcinogenesis

3.1.3.1-*Periopathogens can induce carcinogenesis alone or in synergism with viruses- P. gingivalis* and *F. nucleatum*, best known for their involvement in periodontitis, have been implicated in the pathogenesis of several chronic diseases, as well as various types of gastrointestinal malignancies e.g. colorectal, pancreatic (66,90,92). Gallimidi established an animal model of chronic P. *gingivalis*/F. *nucleatum* infection-associated oral tumorigenesis. and demonstrated that *P. gingivalis*/*F. nucleatum* chronic infection promotes the growth and severity of 4NQO-induced tongue tumours. Augmented signaling along the IL-6-STAT3 axis is speculated as underlying for carcinogenic effect. This work made probably the first documentation of the direct effects of periopathogens causing stimulation of epithelial derived cancerous cells via TLR 2 signalling and promoting carcinogenesis by IL-6 production (120).

Another group of workers have suggested that orodigestive cancer mortality is related to periodontitis and to the periodontal pathogen, P.*gingivalis*, independent of periodontal disease. Periodontitis-associated mortality was in excess for colorectal. (RR 5 3.58; 95% CI 5 1.15–11.16) and possibly for pancreatic cancer (RR 5 4.56; 95% CI 5 0.93–22.29). Greater serum P.gingivalis IgG tended to be associated overall with increased orodigestive cancer mortality (P trend 5 0.06); P.*gingivalis* associated excess orodigestive mortality was also found for healthy subjects not exhibiting overt periodontal disease (RR 5 2.25; 95% CI 5 1.23–4.14) (121).

3.1.3.2-*Periodontal bacteria and viruses may act synergistically to cause periodontitis* (15,122-124). The bacterial pathogens that cause periodontal disease are known to cause epigenetic modifications to the genomes of EBV, KSHV, and HIV and may modify other viral genomes as well. Another example of a virus that may be affected bacterial epigenetic modulation is HPV16. HPV16 transcription, mediated by the E2 protein, is reduced by CpG methylation of the E2 binding sites in cervical epithelial cells (125). HPV hypomethylation is associated with cervical cancer progression, as progressively less methylation was seen in patients with carcinoma than in patients with precancerous lesions and asymptomatic infection (126). Furthermore, cell lines derived from HPV-associated HNSCCs have increased DNMT3A expression and cellular DNA methylation in regions containing genes and LINE 1 elements compared to cell lines from HPV-negative HNSCCs (127). It has been suggested that streptococci in the oral cavity promote the development of HPV-associated HNSCC through stimulation of the host inflammatory response and production of carcinogenic metabolites, such as acetaldehyde (128). Taken together, these studies suggest an additional link between bacteria and HPV associated cancer (129).

3.1.3.3-*Periodontal pockets can act as reservoirs of putative carcinogenic strains* - In this biofilm life style, physiologically diverse organisms successfully co-exist via continuous adaptation. Microorganisms coordinately respond to their local environment including other microbes, nutrient flux etc.and develop sophisticated intraspecies and ⁄ or interspecies communication mechanisms (130). Patients with periodontitis demonstrated a significantly higher percentage of *H. pylori* in plaque (79% *vs*. 43%) and in the stomach (60% *vs*. 33%) than in periodontally healthy patients ($p < 0.05$). The co-existence of *H. pylori* in both dental plaque and the stomach was detected in 78% of patients, indicating that the oral cavity could be a potential reservoir for transmission of and re-infection with *H. Pylori* (100). The primary extra-gastric reservoir for *H. pylori* has been reported to be the oral cavity (101, 131-133). *H. pylori* was detected significantly more frequently in salivary (23.5%) and subgingival (50%) samples of subjects with periodontitis than from healthy subjects (7.3% and 11.4%, respectively, $p < 0.05$). In subjects with chronic periodontitis *H. pylori* was detected frequently, suggestive of colonization by this species when periodontal pocketing and inflammation are present (102).

The rich environment of the periodontal pocket could favor the colonization of many microbes including *H. pylori*. Progressive chronic inflammation and the diversity of periodontal pathogens could provide a range of nutrients and binding sites for other microorganisms. *Fusobacterium* species have been reported as key microorganisms in initiating co-aggregation amongst genera of initial colonizers of the plaque biofilm and also with *H. pylori* amongst other pathogens in subgingival plaque biofilm (64,134) similar observations have been documented about some viruses also e.g human papilloma virus (HPV), cytomegalovirus, and Epstein-Barr virus (EBV) also, which are known as potential carcinogenic agents. EBV, however has been linked to cancer including lymphoma and nasopharyngeal carcinoma (15,135,136).

3.1.3.4-*Microbial metabolic end products e.g reactive oxygen species , nitrosamines and acetaldehyde* etc. - Nitrosamines have been linked to cancers of the stomach and esophagus ,which have further been associated in situations of poor oral hygiene (76). Accumulation of carcinogenic metabolites produced by periodontopathogenic bacteria such as endotoxins (lipopolysaccharides), enzymes (proteases, collagenases, fibrinolysin, and phospholipase A) and metabolic byproducts (hydrogen sulfide, ammonia, and fatty acids) are toxic to surrounding cells and may directly induce mutations in tumour suppressor genes and proto-oncogenes or alter signaling pathways that affect cell proliferation and/or survival of epithelial cells (79).Various investigators have proposed that oral ecological

shifts accompanying periodontal disease are characterized by proliferation of ketone-producing and nitrate-reducing microorganisms. The latter may contribute to increases in carcinogen concentrations (137), which is consistent with evidence of oral metabolism of alcohol to acetaldehyde by candida sps. and streptococcus sp (68,138). Poor oral hygiene as is frequently found in subjects with periodontal disease increases the production of acetaldehyde, a known carcinogen, from ethanol in saliva (139,140). Similarly, P. gingivalis produces an enzyme, l-methionine-alpha-deamino-gammamercaptomethane- lyase (METase), that degrades methionine to methyl mercaptan. Methyl mercaptan is a carcinogen that also contributes to P. gingivalis pathogenicity in periodontitis (141,142).

Volatile sulfur compounds (VSCs), mainly composed of hydrogen sulfide (H2S) and methyl mercaptan (CH3SH) are found to be associated with periodontal pockets and recently, have been explored to have roles in periodontal disease progression being toxic metabolites.VSCs increase the permeability of a model for gingival crevicular epithelia, inhibit the proliferation of human gingival fibroblasts (HGF), human gingival epithelial cells (HGEC) and osteoblasts. H2S also causes apoptosis in HGF and HGEC. Very low concentration of H2S at lower concentration in periodontal pocket causes genomic DNA damages in both HGF and HGEC. It has been suggested that VSCs may be one of the contributing factors for carcinogenesis because of increasing oxidative stress, and as the Ras/mitogen activated protein kinase signaling pathway, which is constitutively activated in many types of cancer, is enhanced (143).

3.1.3.5-*Bacterial/viral infections regulating gene expression*- Epigenetic modifications can occur on both human and viral genomes by various bacterial metabolites. HIV and herpes viruses, including Kaposi's sarcoma-associated herpesvirus (KSHV) and Epstein-Barr virus (EBV), establish lifelong latent infections in their host cells. KSHV, EBV, herpes simplex virus 1 (HSV-1), and HIV latency and reactivation are controlled by epigenetic modifications (144-147). Viruses and bacteria have developed diverse mechanisms to directly affect host cell epigenetics, driving pathogenesis and oncogenesis .Bacterial butyric acid levels can be up to 20 mM within the gingival pocket (148-150). Different groups of researchers have suggested that products secreted by *P. gingivalis*, including butyrate, induce acetylation of histones within neighboring cells (148,151,152).

P. gingivalis metabolites, but not those of Gram-positive organisms, were able to enhance KSHV replication Bacterium-mediated KSHV reactivation coincided with increased global acetylation of H3 and H4, suggesting the bacterial supernatant contains HDAC inhibition properties. Bacterium-induced HDAC inhibition leading to viral reactivation has been observed for EBV also. One protein controlling EBV reactivation is ZEBRA, a lytic gene transactivator and the product of the BZLF1 gene. In Daudi cells latently infected with EBV, ZEBRA expression was increased by *P. gingivalis* spent medium, triggering viral reactivation (153,154). Butyrate is an HDAC inhibitor and has been implicated in the reactivation of HIV and EBV (153,155,156). However, butyrate may not be the only *P. gingivalis* product involved in epigenetic regulation, as differences were found between cellular epigenetic changes induced by *P. gingivalis* and *F. nucleatum*, another *Bacteroidete* anaerobe which produces butyrate. While global H3K4me3 decreased with *P. gingivalis*, H3K4me3 did not decrease in gingival cells incubated with *F. nucleatum* (157). In addition, *P. gingivalis* produces LPS, and LPS-induced Toll-like receptor (TLR) signalling leads to widespread changes in the epigenetic profiles of TLR-responsive genes (158,159). Gingipains, membrane vesicles and other short chain fatty acids, such as propionic and isobutyric acids, are also produced by *P. gingivalis* and may affect epigenetics (129).

3.1.3.6- *Salivary genotoxicity induced by polymicrobial oral biofilms*- Poor oral health has

been shown to associate with the genotoxic salivary activity. Bloching et al (160) reported a significant association (p≤0.05) between high-plaque index and high number of carious teeth with the genotoxic activity in saliva. The polymicrobial burden caused by oral biofilms was suggested to contribute towards the mutagenic interactions with saliva which could promote carcinogenesis as co-factors (161).

3.1.4-Mechanistic Basis Supporting a Role for specific periodontal bacteria in Cancer

Both *P. gingivalis* and *F. nucleatum* establish, the two most documented and studied periopathogens have typically intracellular persistence within epithelial cells, can spread systemically and cause extra-oral infections, and have well-characterized immune disruptive properties (162). *F. nucleatum* is strongly proinflammatory and have been extensively studied in association of colorectal cancers (CRC). McCoy et al (91) demonstrated a positive correlation between mRNA levels for several local cytokines and *Fusobacterium* species in CRC cases. Another investigation revealed the role of bacterium in generating the proinflammatory environment for tumour progression in the $Apc^{Min/+}$ mouse model of intestinal tumorigenesis (90). *P. gingivalis* significantly impacts the local defense mechanisms in periodontal pockets and can exhibit both pro- and anti-inflammatory properties, depending on the context (163,164). Moreover, both these pathogens are capable of disrupting the epithelial cell signaling which is of relevance to cancer progression, epithelium being a barrier tissue .

3.1.4.1-*Porphyromonas gingivalis*- Mao S et al studied the effects of *P.gingivalis* in primary cultures of gingival epithelial cells and reported its strongly antiapoptotic action (165).The bacterium lead to the activation of Jak1/Akt/Stat3 signaling, esponsible for controlling mitochondrial apoptosis (165),(166). At the mitochondrial membrane, the activity of proapoptotic Bad was inhibited, and there was an increased ratio of Bcl2 (antiapoptotic):Bax (proapoptotic) affecting cytochrome c (167). An alternate mechanism for inhibition of apoptosis in epithelial cells by *P. gingivalis* was documented by Moffatt CE et al , who reported an up-regulation of miR-203 leading to inhibition of the negative regulator SOCS3 and subsequent suppression of apoptosis (168). *P. gingivalis also* prevents ATP-dependent apoptosis mediated through the purinergic receptor $P2X_7$ by secreting a nucleoside diphosphate kinase (NDK) (169) in addition NDK was also thought to be responsible for impeding activation of the NLRP3/ASC/caspase-1 inflammasome, further reducing secretion of IL-1β, which is considered significant in carcinogenesis for the priming of IFNγ-producing tumor–antigen-specific $CD8^+$ T cells (170).

P. gingivalis affects the S-phase of the cell cycle by manipulation of cyclin/CDK (cyclin-dependent kinase) activity and reducing the level of the p53 tumor suppressor (171). Through extracellular secretion of gingipains, activates Protease Activated Receptor (PAR) leading to promatrix metalloprotease (MMP)-9 and mature MMP-9 production , along with nucleoside diphosphate kinase (NDK), which cleaves ATP and prevents activation of the proapoptotic $P2X_7$ receptor. Intracellular *P. gingivalis* activate antiapoptotic Jak-Stat signaling and inhibit expression of the p53 tumor suppressor. Additionally, Erk 1/2 and p38 are activated, which also elevates proMMP-9 expression.

P. gingivalis induces the expression of the B7-H1 and B7-DC receptors in both primary gingival epithelial cells and OSCC cells (172). B7-H1 expression could contribute to immune evasion by oral cancers as it suppresses effector T cells through regulatory T cells . Another impact of *P. gingivalis* on OSCC cells is in promoting cellular invasion. *P. gingivalis* infection activates the ERK1/2-Ets1, p38/HSP27, and PAR2/NF-KB pathways to induce promatrix metalloproteinase (MMP)-9 expression (173). Gingipains, cysteine proteinases produced by *P. gingivalis* engage the PAR2 receptor and cleave the MMP-9 proenzyme into the mature active

form. MMP-9 degrades basement membrane and extracellular matrix, which promotes carcinoma cell migration and invasion, thus contributing to OSCC metastasis.

3.1.4.2-*Fusobacterium nucleatum*

Epithelial cell responses to *F. nucleatum* infection are also consistent with carcinogenesis Signaling molecules targeted by *F. nucleatum* include several cyclin dependent kinases (CDKs) involved in cell cycle control, and, as a result, *F. nucleatum* can elevate cell proliferation and migration (174). *F. nucleatum* also activates p38, leading to the secretion of MMP-9 and MMP-13,which contributes to tumor invasion and metastasis. Recently, Rubinstein MR etal demonstrated fusobacterial adhesin FadA binds to E-cadherin on colon cancer cells and activates β-catenin signaling (92). This pathway leads to increased transcriptional activity of oncogenes, Wnt, and pro-inflammatory cytokines, as well as stimulation of CRC cell proliferation. the observations were supported by the in vivo finding that *fad A* gene levels in colon tissue from patients with CRC were >10-fold higher compared with normal individuals.

3.1.4.3-*Candida albicans* - A series of classic studies implicated the role of candida in oral carcinogenesis as the fungus was known to produce nitrosamines, that could act alone or in combination with other chemical compounds as carcinogens (175-177). These agents could activate specific proto-oncogenes that could trigger the development of a cancerous lesion and /or are capable of triggering dysplastic changes in the oral epithelium or carcinoma (178). C. albicans also produces acetaldehyde from ethanol metabolism by alcohol dehydrogenase enzyme .The compound is toxic, mutagenic and indisputably carcinogenic, owing to its ability to impart structural, functional alterations in DNA, impact on it s replication and repair and therefore, it is a risk factor for carcinoma (179).There are a no. of additional pathways which may potentially link candida to favor metastatic progression of cancer e.g via the induction of an inflammatory process , molecular mimicry, and the Th17 response of immune system. Further, recent investigations have provided cumulative evidence that C. albicans is even able to stimulate the onset and development of cancerous processes (68,180).

3.2-Periodontal immune-inflammatory response aspects - The dysregulated immuno-inflammatory response in periodontal tissues, being the central pathogenesis of chronic periodontal disease serves as a reservoir of noxious metabolic products including living and necrotic cells, cytokines, chemokines, prostaglandins, MMPs, reactive oxygen and nitrogen radicals to the local and systemic tissues (181). Accumulation of these compounds may likely modulate the tumor microenvironment by causing DNA damage, promoting epigenetic and genetic alterations, increasing angiogenesis, cell survival, proliferation, migration, and inhibiting apoptosis. There is a mounting evidence that documents subversion and dysregulation of these complex system of signaling molecules during the onset and progres- sion of malignant disease. Overall, altered chemokine function in cancer promotes cell survival, enhanced proliferation, neovascularization, motility and metastasis in multiple tumor types. Lappin and colleagues found significantly higher levels of circulating CXCL5 in smokers with periodontitis, which correlated with probing depth, attachment loss, and tobacco consumption (182). The authors suggested of the role of CXCL5 as a potential promotor of tumorigenic progression ,looking at this compound as a pro-angiogenic factor ,together with its role to promote tumor cell growth and motility (183). Here, we will focus specifically on chemokines and receptors that are expressed in periodontal tissues and potentially can have a modulatory role in the tumor microenvironment.

3.2.1-*IL-8 (CXCL8*) - Many periodontal bacteria and bacterial products stimulate IL-8 production from a variety of cells from periodontal tissues .

IL-8 is, infact one of the most salient and significant chemokine involved in periodontal immune response. Yang L et al conducted a meta analysis investigating the risk of oral cancer in patients with polymorphisms of the IL-8-251A>T locus revealed that Caucasians harboring the AA genotype were more susceptible to the risk of malignancy (184), whereas a separate meta-analysis by Wang Z etal documented a higher risk for people with either the AT or AA genotype (185). Some recent investigations have revealed the role of IL-8 as an autocrine regulator of OSCC growth(57) and found this compound responsible for enhancing cell mobility (186). Salivary IL-8 has been proposed to be a discriminative biomarker for oral cancer by Spielmann N et al (56,187).

3.2.2-*Interleukin (IL)-6*-is a pro-inflammatory cytokine that mediates chronic inflammation and may play an important role in inflammation-driven oral carcinogenesis (188). IL-6 activates inner-cellular transcription factors like , (STAT)-1 and STAT3 by phosphorylation .High STAT3 levels have been observed in various tumors, linking IL-6 to tumorigenesis (189-191). IL-6 is thought to have regulating effects on cell survival, growth, proliferation, and differentiation of cancer cells and is associated with tumorigenesis, angiogenesis, and cachexia (192-194). It has also been shown that OSCC cells preferentially invade and metastasize into IL-6-rich environments (195). Numerous studies suggest that IL-6-induced inflammation and carcinogenesis may be in part orchestrated via epigenetic changes (3,196,197) DNA methyltransferase (DNMT1) maintains the methylation pattern, when the IL-6 level is low, the p53 promoter region is modified by DNMT-1 and thus p53 expression decreases. The disrupted expression of this tumour suppressor gene plays a key role in cancer initiation (198).

3.2.3-CC-chemokines- CC-chemokines have been documented to have significant bearing in the pathogenesis of periodontitis , mostly acting as chemotactic for kinds of immune cells involved e.g monocytes and lymphocytes (CCL2andCCL3), CD4+ T cells (CCL4), Th1cells(CCL5).usually these are observed in high concentrations in diseased tissues and found to be related to disease activity (199,200). Many of thes chemokines have been studied in association of carcinogenesis e.g. CCL5–CCR5 signaling is reported to enhance OSCC motility, as well as increasing production of the gelatinase, MMP9 (202). Ferris and coworkers (201) documented loss of CCR6 and upregulation of CCR7, the receptor for CCL19 and CCL21, on oral cancer cells, and demonstrated that this was related to lymph node metastasis. Another investigation from Li and colleagues (203) demonstrated CCL2 production by cancer- associated fibroblasts (CAFs), which stimulated production of reactive oxygen species (ROS) in cocultured oral cancer cells. Further CCL2 production in CAFs was enhanced by ROS, leading to a vicious environment for production of both the mediators.

3.2.4-CXCL proteins - CXCL 5 protein, known as a chemotactic factor for neutrophils,has also been implicated in tumour angiogenesis, cancerous cell growth . Invivo studies demonstrate when CXCL5 expression was suppressed in OSCC cells, there was observed a complete blockage of tumourigenic phenotype of cells (204). Khurram and colleagues reported higher levels of both CXCR1 and CXCR2 in oral cancer (205). These IL8 receptors have an ability to bind multiple CXC-chemokines including CXCL1, CXCL2, CXCL3, CXCL5, and CXCL and cause coincidental simultaneous activation of these pathways in carcinogenic environment.

The CXCL12(SDF-1)/CXCR4 axis also appears to play critical roles in OSCC development and progression. Expression of the CXCR4 receptor has been observed at higher levels in metastatic tumor cells as compared to non-metastatic (206). SDF-1/CXCR4-driven invasion of oral cancer is reported to be dependent upon NFkB signaling (207,208). Tang CH et al has proposed CXCR4-mediated upregulation of IL-6, secreted by the tumor cells to stimulate osteo-clastogenesis (209), pointing to its role in enhancing invasion of the tumour. Studies by

Oue et al (210) provided further evidence of a role for IL-6 and RANKL in OSCC, mediated at least in part through a CXCL2- dependent mechanism.

3.2.5-TLR recetors- TLR9 expression was reported to be significantly elevated in the tissues of oral squamous cell carcinoma as well as periodontitis, and increased receptor expression was correlated with increased tumor size and clinical stage (211,212). In vitro studies revealed that activation of TLR9 can mediate oral cancer cell migration by up-regulating MMP2, and tumor cell proliferation by up-regulating cyclinD1expression,both in an AP-1-dependent manner (212,213). Increased IL-1α and IL- 6 productison in OSCC cells treated with a TLR 9 agonist was also reported (212). TLR 9 activation is thought to contribute towards carcinogenesis by enhancing inflammation and through modulating cell cycle progression. Another clinical investigation reported a strongcorrelation between TLR2,-4, and-9 expression and increased tumor invasion in oral tongue squamous cell carcinoma. The mediators involved in the process were all similar to the periodontal disease mediators expressing through NF-κB,AP-1,and MAPKs (213). NF-κB expression and activity was observed very relevant in oral cancers, with protein levels gradually increasing with progression of lesion from premalignant to the invasive form (214-216). Further,aberrant function of NF-κB has also been reported to stimulate STAT3 activation,which is a significant player in tumour invasion by an autocrine /paracrine mechanism in SCC (56)

3.2.6-RAGE receptors- the receptor for advanced glycation end products (RAGE), a multi-ligand receptor expressed on various cell membranes, has been suggested to play a role also in oral infection-systemic health associations and carcinogenesis (217). This receptor is associated with proinflammatory responses and may underlie in diverse pathologies including periodontal disease (218). Oral infection may also directly reflect in endothelial dysfunction with systemic consequences .The cytokine reactions involved have been shown to play a role in the immune-related mechanisms of cancer development (161). Also of interest is the relationship between the pro-inflammatory expression of the receptor for advanced glycation end products (RAGE) and esophageal, gastric, colon, biliary, pancreatic, and prostate cancers. RAGE has been shown to play a role in the inflammatory processes of oral infections including periodontal disease (76).

3.2.7-The integrin αvβ6 - is not expressed in healthy epithelia, but upregulated in cancer, with possible progression of carcinogenesis, and during wound healing, modulating the expression of matrix metallo-proteinases and activating TGF-β. Mechanisms that tip the balance between tumor dormancy and multistage carcinogenesis *via* immune mediated responses are poorly understood (219). T antigen-specific CD4+ T cells are able to induce anti-angiogenic chemokines *via* TNFR1 and IFN-gamma signalling and prevent the expression of integrin αvβ3, tumor cell proliferation, angiogenesis and multi-stage carcinogenesis, preserving T antigen-expressing pancreatic islet cells. It is relevant that in the absence of TNFR1 and IFN-gamma signalling, the same T cells are capable of promoting angiogenesis and multistage carcinogenesis. These cells are seen selectively in the tumor microenvironment around pancreatic islets where they may arrest or promote the transition of islets that are dysplastic into islet carcinomas (64).

3. 3-Shared risk factors - Another important aspect to understand the association of periodontal inflammation and carcinogenesis is the likely sharing of common risk factors. Most of the risk factors like smoking, socio-economic status, diabetes, age, gender and ethnicity, along with genetics have primarily similar associations to both the disease conditions and have been documented as major confounding factors in various epidemiologic observations (76).

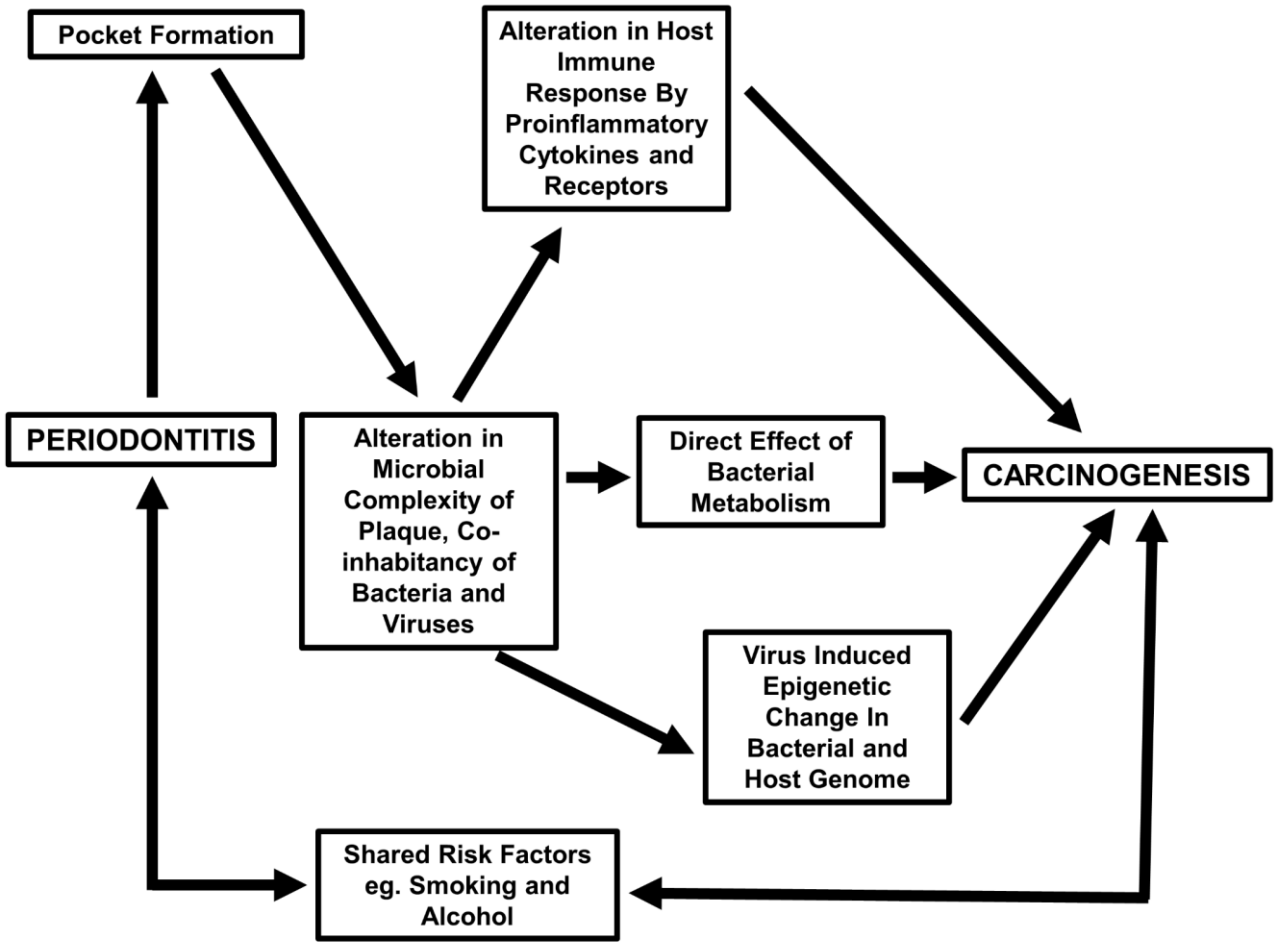

Figure 1 – Schematic overview of mechanisms linking periodontal disease and carcinogenesis. Periodontal disease causes deepening of gingival sulcus i.e pocket formation ,which provides a sheltered area for microbial accumulation and changes the local microenvironment to affect the microbial ecology. Alterations in flora including co-inhabitance of complex and different microbes like gram negative bacteria , fungi and viruses contribute towards carcinogenesis (15,120-124). Microorganisms alone or in symbiotic association with other microbes promote and potentiate carcinogenesis by direct toxic effects of their metabolites (68,141-143) and by evoking a host response mediated by a variety of inflammatory cytokines. Apart from these pathways, both disease conditions share many common risk factors such as smoking and alcohol (76).

4-IMPORTANT CONSIDERATIONS AND FUTURE CONCERNS - A direct association between co-existing diseases requires cautious interpretations Variables such as consumption of tobacco, alcohol; personal factors such as nutrition, stress, socioeconomic status, immune status and body mass index make it difficult to obtain clear correlations. Published literature suggests many studies have utilized tooth loss ,as an indicator of periodontal disease ,which needs to be ascertained in future studies ,keeping in view all other confounding factors for tooth loss. Some considerations regarding periodontal disease, such as use of specific case-definitions, the relevance of disease aggression, potential for inducing a systemic inflammatory burden and systemic complications; and whether or not all forms of periodontal diseases would predispose individuals to the risk of carcinogenesis are important. A pertinent point in this context may well be related to volume with regard to size of the inflammatory burden, based on disease severity, number of teeth affected and inflammatory status at the time of

examination. Thus, more research is needed to specifically qualify different types of periodontal disease, their association with systemic diseases such as cancer, and a possible causal role. Though it sounds quite convincing, to say that a large inflammatory loading attributed to periodontal disease could correlate with cancer risk, by virtue of the various underlying mechanisms involved as depicted in Figure 1, but quantification of an association between periodontal disease and cancer and other systemic diseases would essentially needs more regulated, controlled , well planned, standardized observational and interventional investigations in future (64,220).

5-CONCLUSION AND CLINICAL RELEVANCE

Chronic periodontitis may represent a clinical high-risk profile for initiation and progression of carcinogenesis in humans. Although validation through further prospective studies is essential, but looking at the high prevalence of periodontal disease ,it seems that controlling or treating chronic periodontal inflammation may prove to bear a significant impact in reducing overall incidence and prevalence of human cancers. Prevention and treatment of periodontitis may have substantial implications for public health in terms of prevention and early diagnosis, improving the prognosis and survival rate and reducing the morbidity and mortality associated with human cancers. Patient care could be improved with close liaison between oncologists and periodontists. It would be meaningful to categorize periodontal disease at the time of cancer diagnosis which may bear interesting dimensions for medical oncologists, in terms of periodontal disease aggression at the time of diagnosis and cancer outcome with varying aggression of periodontal diseases. Understanding the roles of each type of cell and signalling pathway involved in cancer initiation and progression may pave the path for the discovery of biomarkers specifically targeting cancer inflammation. Epigenetic mechanisms have clearly emerged as important contributors in the pathogenesis of various human cancers. Since these alterations occur frequently and are potentially reversible, this makes them ideal for exploitation as therapeutic targets in cancer management therapy.

Abbreviations:

CAFs, Cancer- associated fibroblasts;
CCL2, CC-chemokine ligand 2;
CDKs, Cyclin dependent kinases;
CH3SH, Methyl mercaptan;
COX2, Cyclooxygenase 2;
CRC, colorectal cancers;
DNMT, DNA methyltransferase;
EBV, Epstein Bar virus;
F. nucleatum, Fusobacterium nucleatum;
H_2S, Hydrogen sulphide;
HBV, Hepatitis B Virus;
HCV, Hepatitis C Virus;
HGEC, Human gingival epithelial cells;
HGF, Human gingival fibroblasts;
HNSCC, Head and neck squamous cell carcinoma;
HPV, Human papilloma virus;
HPV, Human papilloma virus;
HTLV-1, Human T-Cell Lymphotropic Virus;
iNOS, inducible nitric oxide synthase;
KSHV, Kaposi's Associated Sarcoma Virus;
METase, l-methionine-alpha-deamino-gammamercaptomethane- lyase;
MMP, Matrix metalloprotease;
NDK, nucleoside diphosphate kinase;
NDK, Nucleoside diphosphate kinase;
NDK, Nucleoside diphosphate kinase;
OSCC, Oral squamous cell carcinoma;
P. gingivalis, Porphyromonas gingivalis;
PAR, Protease Activated Receptor;
RAGE, Receptor for advanced glycation end products.
ROS, Reactive oxygen species;
STAT3, Signal Transducer And Activator Of Transcription 3 (Acute-Phase Response Factor);
TGFβ, transforming growth factor β;
VSCs, Volatile sulfur compounds;
WHO, World Health Organization;

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