Periodontitis and oral cancer - current concepts of the etiopathogenesis

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Abstract

Gingival tissues are attacked by oral pathogens which can induce inflammatory reactions. The immune-inflammatory responses play essential roles in the patient susceptibility to periodontal diseases. There is a wealth of evidence indicating a link between chronic inflammation and risk of malignant transformation of the affected oral epithelium. Periodontitis is associated with an increased risk of developing chronic systemic conditions including autoimmune diseases and different types of cancers. Besides, some risk factors such as smoking , alcohol consumption and human papilloma virus have been found to be associated with both periodontitis and oral cancer. This review article aimed to study the current concepts in pathogenesis of chronic periodontitis and oral cancer by reviewing the related articles.

Introduction

Rudolf Virchow was the first to indicate a possible link between inflammation and cancer in the 19th century. He noticed leukocyte infiltration in tumor microenvironment and proposed that chronic inflammation can drive cancer development.[1] Genetic modifications can alter the normal control of cell growth and survival, therefore, result in cancer development. In head and neck area these genetic alterations can be induced by different factors including smoking, alcohol and sunlight.[2] Accumulating evidence has also revealed the role of microorganisms in tumor growth in different organs.[3] Gingival tissues are highly vulnerable to oral microbial attacks. The immune-inflammatory responses play essential roles in the patient susceptibility to periodontal diseases.[4-6] Keratinocytes of the gingival epithelium can produce and secret several immune response mediators such as cathelicidins, human defensins (hBDs), chemokines, pro-inflammatory cytokines, and angiogenetic proteins.[7,8] Besides, gingival keratinocytes can recognize pathogen-associated molecular patterns (PAMPs) via receptors, such as toll-like receptors (TLRs).[9]

Periodontitis is associated with an increased risk of developing systemic conditions such as autoimmune diseases and different types of cancers.[10,11] Different factors such as dental calculus, overhang restorations, tooth position, smoking, nutrition, diabetes mellitus, blood dyscrasia, age and genetic alterations have been considered as predisposing factors of periodontal disease.[12] There is now a wealth of evidence indicating a link between chronic inflammation and malignant transformation of the affected oral epithelium.[5,13-15] For instance, malignant transformation of oral lichen planus, a chronic inflammatory lesion, has been reported.[13,15] Oral squamous cell carcinoma (OSCC) represents up to 90% of all oral malignancies and is the main cause of cancer-related deaths.[13-17] Some factors such as tobacco, alcohol, betel quid ingestion, malnutrition, viral infections and oral microbiome have been proposed as the risk factors.[18-20] This review aimed to assess the link between periodontitis and oral cancer with a special focus on the recent advancements in the correlation between chronic periodontitis and oral cancer.

Search strategy

The literature search was conducted through PubMed, Scopus database, and Google Scholar. Studies published since 1995 to 2019, with full text available, were considered for inclusion. For further evaluation, research articles describing periodontitis, periodontal-related disease drivers, periodontitis and systemic diseases, oral cancer and the mechanisms of tumor development were selected.

The contribution of microorganisms to carcinogenesis

Different viruses contribute to the development of cancers. For instance, the association between human papilloma virus (HPV) and cervical cancer and oropharyngeal cancer has been demonstrated. Also, the association between Epstein-Barr virus (EBV) and Hodgkin's lymphoma has been reported.[21,22] In addition to viruses, research has established a strong link between cancer and bacteria. *Helicobacter pylori* (*H. pylori*) is one the most well-recognized pathogenic bacteria associated with cancers such as stomach and intestine cancers.[23,24] Also, the intestinal dysbiosis promotes hepatocarcinogenesis.[25] *Porphyromonas gingivalis* (*P. gingivalis*) which colonizes in the oral epithelium is associated with digestive system cancers.[26] Interestingly, *P. gingivalis* has been indicated in gingival SCC tissue samples.[27]

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The role of oral microbiome and inflammation in periodontitis and oral cancer

Antony van Leeuwenhoek first recognized the oral microbiome in the late 1670s.[28] Oral microbiome has an essential role in inflammatory responses in the head and neck area including oral cavity.[5,6,18,29] Oral microbime is the main cause of periodontitis. The effects of oral microbiota on oral epithelial barrier have been observed. In periodontitis, bacterial pathogens trigger inflammatory responses which result in the destruction of supporting tissues.[29,30] Among the oral microbiome, three specific bacteria have been found as etiologic factors for periodontitis: *Aggregatibacter actinomycetemcomitans* (formerly *Actinobacillus actinomycetemcomitans*), *P. gingivalis,* and *Tannerella forsythia* formerly *Bacteroides forsythus*.[31] However, *P. gingivalis* is suggested to be the major causative microorganism.[32] A positive association between oral health and autoimmune disorders such as diabetes mellitus type-1 and rheumatic diseases has been demonstrated.[33] Also, the role of periodontal infection in cancer risk has been recorded. For example, in an earlier report, the association between periodontal pathogens mainly *A. actinomycetemcomitans* and gastric precancerous lesions such as chronic atrophic gastritis, intestinal metaplasia, or dysplasia had been indicated.[34] Moreover, it has been shown that some species of human oral bacteria such as *Fusobacterium nucleatum* or Bacteroides are associated with periodontitis, appendicitis and colorectal cancer.[35] Interestingly, oral microbiome varies in patients with different types of cancer. For example, in patients with esophageal cancer, *Treponema denticola*, *Streptococcus mitis*, and *Streptococcus anginosus* are the main microorganisms, however, *Fusobacterium nucleatum* is the main component of oral microbiome in the patients with colorectal cancer.[36] In addition, *P. gingivalis* and the Fusobacterium species have been found in esophageal cancer, colorectal carcinoma and pancreatic cancer.[37-40] In a previously published paper, the positive association between periodontal diseases and non-Hodgkin lymphoma (NHL) has been demonstrated. The authors suggested the periodontal disease as a risk factor for NHL. Besides, they indicated an inverse association between tooth loss and NHL. They proposed that tooth loss may result in the resolution of local oral inflammation due to the oral microbiome and the immune responses.[41] Nonetheless, a formerly published meta-analysis has found the tooth loss as a risk factor for esophageal cancer.[42] According to the Hill's criteria, tooth loss is a marker for esophageal cancer not a causative factor.[43] Also, a previously published work has indicated that bone loss associated with periodontitis is a risk factor for the development of oral cancer.[44] Importantly, oral pathogens such as streptococci (*Streptococcus intermedius*, *S. constellatus*, *S. oralis*, *S. mitis*, *S. sanguis*, *S. salivarius*) have been isolated from cervical lymph nodes in patients with oral cancer.[45] The association between *H.pylori* and oral cancer has also been suggested.[18,46] In addition, a recent meta-analysis has demonstrated the association of *H. pylori* with periodontitis.[47] Previous studies have suggested that the metabolism of alcohol and formation of acetaldehyde, a major carcinogene, by oral microbiome such as yeast, has a great impact on the risk of head and neck cancer, especially oral cancer.[48] Bacterial species in the oral cavity of patients with periodontitis turn nitrate into nitrite or produce acetaldehyde which all are carcinogenic metabolites.[49] Besides, in periodontal diseases, carcinogens produced by tobacco smoking and alcohol consumption, penetrate to the underlying tissues.[50] It is suggested that microbiome induces cancer growth through the interaction of multiple signaling pathways.[51] Table 1[11,33,41,52-64] shows a list of autoimmune disorders and different types of cancer associated with periodontitis.

Possible signaling pathways involved in microbial carcinogenesis

Several previous studies have demonstrated the chronic inflammation as a risk factor for malignant transformation in organs such as the oral cavity, head and neck area, esophagus, stomach, liver, colon, uterine cervix, ovaries, urinary bladder and lung.[65] It is suggested that the inflammatory response and cell-stimulating signals provide a microenvironment for cell proliferation and differentiation.[66] Chronic inflammation can induce cell proliferation and mitogenic activities via the activation of signaling pathways such as MAPK/ ERK.[67] Besides, chronic inflammation can inhibit apoptosis by modulation of the expression of Bcl-2 family.[68] It is proposed that persistent infections are able to induce DNA damage in proliferating cells through the production of toxic substances such as reactive oxygen species (ROS) and reactive nitrogen intermediates (RNI) by inflammatory cells. Consequently, tissue regeneration results in DNA damage and permanent genomic alterations in proliferating cells.[69] Cytokines and chemokines have essential roles in tumor initiation and progression.[70] Activation of pro-inflammatory cytokines such as IL-6, IL-8, IL-1β, and TNF-α has been demonstrated in cancers.[71] Miroorganisms can induce cancer growth through different pathways. It has been proven that hepatitis B virus (HBV) and hepatitis C virus (HCV) cause hepatocellular carcinoma. Some of underlying mechanisms of carcinogenesis in HCV associated liver cancer include increased hepatocyte proliferation, induction of immune and inflammation responses and genomic mutations.[72] In the oral cavity, traumatization of oral epithelium during mastication results in HPV infection of oral epithelial basal cells. Later, HPV reaches the superficial layers. Elevated expression of E6 and E7, the main contributors to microbial-induced cancer, has been noticed during HPV infection.[73] In addition, HPV interrupts the initial phases of the immune response, including the expression of TLRs and cytokines which have great impacts on HPV recognition.[74] Deep periodontal pocket is a niche for viral infections, such as HPV,[75] EBV[76] and HSV.[77] Besides, the presence of HPV E6/E7 mRNA in periodontium may support the hypothesis that periodontal tissues function as a reservoir for latent HPV infection.[78]

Similar to viral infections, bacterial infections can cause inflammation and alterations in the microenvironment. Bacteria produce different mediators which promote cell proliferation, mutagenesis and angiogenesis. Additionally, bacteria inhibit cellular apoptosis. Some bacteria such as *H. pylori* invade the gastric

Table 1. List of autoimmune disorders and different types of cancer associated with periodontitis.

Autoimmune disease (reference no.)	Cancer type (reference no.)
Rheumatoid arthritis (11,33)	Pancreatic cancer (52)
Type 2 diabetes mellitus (33,53)	Orodigestive cancer (54)
Alzheimer's disease (55)	non-Hodgkin lymphoma (41)
Systemic lupus erythematosus (56)	Lung Cancer (57)
	Head and neck SCC (58)
	Breast cancer (59)
	Prostate cancer (60)
	Proximal colorectal neoplasms (61)
	Oral cancer (62,63)
	Gastrointestinal cancers (64)

mucosa and gastric lymph nodes, therefore, intiate and develop a chronic infection.[18] *H. pylori* infection induces IL-1β production, the etiological agent for gastric cancer.[79] IL-1β is a critical mediator of chronic inflammation and several cancers.[80] The role of IL-1β in tumorigenesis, tumor invasiveness, angiogenesis, and metastasis and tumor-host interactions has been demonstrated.[81] The role of IL-1β in periodontitis has also been recorded.[82] *H.pylori* has been indicated in the oral cavity[83] and its prevalence in the oral cavity is related to the progression of periodontal diseases.[84] *A. actinomycetemcomitans* is associated with increased secretion level of TNF-α , IL-1β and other cytokines involved in the inflammatory reactions.[85,86] Inflammatory mediators can disseminate from the oral cavity to various extraoral sites and contribute to the development of different diseases such as cancers in other organs. A previously published work has demonstrated a higher prevalence of proximal colorectal neoplasms in patients with periodontitis.[61] Also, a published paper has indicated that periodontal pathogens and/or inflammatory mediators may promote prostate cancer.[60] These findings may suggest the role of some periodontal microorganisms including *P. gingivalis* in cancerogenesis.[87]

The mechanisms by which *Porphyromonas gingivalis* may promote head and neck cancer

Activation of some immunologic and inflammatory reactions in the host by *P. gingivalis* has been considered as the underlying mechanism. Besides, it has been found that *P. gingivalis* is capable to invade and penetrate different epithelial cells which enables it to alter some genes in response to chronic infection.[88] A very recent investigation has demonstrated that *P. gingivalis* penetrates oral mucosa by targeting Grainyhead-like 2 (GRHL2), an epithelial-specific transcription factor. Later, GRHL2 causes epithelial barrier damage by inhibition of tight junction protein expression which results in increased periodontium tissue destruction.[89] *P. gingivalis* also activates nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) and MAPK pathways in human oral epithelial cells[90] (Table 2). It is hypothesized that chronic infection by *P. gingivalis* can establish a microenvironment by targeting CD274 and programmed cell death 1 ligand 2 (PDCD1LG2) via the activation of STAT1. Moreover, *P. gingivalis* promotes the secretion of cytokines such as IL-6 which in turn activates tumorigenic transcription factors such as STAT1.[70] Additionally, *P. gingivalis* induces the expression of the proenzyme matrix metalloproteinase 9 (proMMP9) and subsequently active form of MMP-9. It is believed that MMP-9 has a key role in the degaradation of tumor microenvironment to promote the invasion and metastasis of cancer cells including OSCC cells.[91] *P. gingivalis* also induces epithelial-mesenchymal transition (EMT) of normal oral epithelial cells by increasing phospho-GSK3ß, an important regulator of EMT.[92] Besides, the presence of *P. gingivalis* is related to high serum level of C-reactive protein (CRP).[93] It has been reported that CRP opsonizes *P. gingivalis* for complement-binding and activates complement.[94] The association between circulating levels of CRP and an increased risk of epithelial cancers including ovarian cancer, breast cancer, metastatic gastric cancer and colorectal cancer has been proved.[95,96] Table 3[97-119] summarizes the molecular mechanisms by which *P. gingivalis* may promote periodontitis and oral cancer.

The role of inflammatory cells in periodontitis and cancer development

Various inflammatory cell types contribute to the inflammatory responses. Macrophages are one of the most important inflammatory cells which have significant roles in the host innate response to periodontal pathogens. Macrophages are classified into two groups: M1-type and M2-type. M1 macrophages are produced in response to Th1-cell-related cytokines such as interferon-γ (IFN-γ)

Table 2. A summary of molecular mechanisms by which Porphyromonas gingivalis may promote periodontitis and oral cancer.

Molecular mechanism
Activation of immunologic and inflammatory reactions (IL-1, IL-6, IL-8, TNF-α)
Penetration of oral mucosa (GRHL2)
Establishment of a microenvironment (CD274)
Establishment of a microenvironment (PDCD1LG2)
Degaradation of tumor microenvironment (MMP9)
Induction of EMT (phospho-GSK3ß)
Opsonization of bacteria for complement-binding and activation of complement (CRP)
Promotion of alveolar bone loss (IL-17A)

Table 3. A summary of the role of inflammatory cells in development of periodontitis and secreted factors.

Inflammatory cell type (no. of reference)	Role in periodontitis	Secreted factors
M1 Macrophages (98,119)	Promotion of host immune defense, digestion of microorganisms, initiation of inflammatory responses	TNF−α, IL−1β, IL−6, CXCL9 and CXCL10
M1 Macrophages (100)	Alveolar bone resorption, osteoclastogenesis and collagen degradation	IL-1β, IL-23, IL-6, TNF-α and MMPs
M2 Macrophages (98,99)	Local tissue repair and wound healing	IL−4 and IL−10
M2 Macrophages (101)	Promote tumor development	IL-10, IL-13 and TGF-β
TAMs (97)	Tumor migration, angiogenesis, invasion and metastasis	IL-4, MIP-1β, CCL18, MMP-9 and VEGF
Mast cells (103)	Enhancement of periodontitis	TLR4
Neutrophil (106)	Improvement of host response to inflammation	LFA-1
Neutrophil (109,110)	Enhancement of periodontal tissue breakdown	Lytic and proteolytic enzymes and MMP-8
T helper cells (112)	Activation of other immune cells such as neutrophils and B cells	IL-1, IL-17E and IL-17
B cells (113)	Promoting inflammatory responses and tumor microenvironment	Antibodies against pathogens
Both T cells and B cells (112)	Alveolar bone resorption	RANKL
Tregs CD4+ T lymphocytes (116)	Suppresion the immune responses and promotion of pathogen survival	CTLA-4), GITR, CD103, CD45RO and Foxp3

and lipopolysaccharide (LPS). M1-type macrophages secrete inflammatory cytokines such as tumor necrosis factor TNF-α, IL-1β, IL-6, and the chemokines CXCL9 and CXCL10. Although M1 macrophages promote host immune defense and digest different groups of microorganisms, at the same time may cause tissue damage. Th2-cell-related cytokines, such as IL-4 and IL-13 can stimulate M2-type macrophages resulting in secretion of anti-inflammatory cytokines such as IL-10. Thus, activation of M2 cells has a great impact on local tissue repair and wound healing. However, M2 macrophages promote tumor development by producing IL-10, IL-13 and TGF-β.[97] Besides, the proportion of M1-type macrophages and M2-type macrophages plays a critical role in the status of gingival tissue and development of periodontitis.[98,99] Inflammatory macrophages also take part in osteoclastogenesis, collagen degradation and alveolar bone resorption by secreting IL-1β, IL-23, IL-6, and TNF-α and enzymes (MMPs).[100] Additionally, interactions between tumor-associated macrophages (TAMs) and cancer cells play important roles in the regulation of tumor microenvironment. TAMs initiate and support tumor development via signaling molecules and pathways such as growth factors, cytokines and chemokines.[97,101]

Mast cells are other key players in inflammatory responses. In a previously published work, a significant increase of mast cell density has been found in periodontitis compared to healthy gingiva. Notably, mast cells were mostly located next to mononuclear cells.[102] A previous study has indicated an increased expression level of TLR4 on mast cells in periodontal tissues of patients with chronic periodontitis.[103] In OSCC, mast cell density increases and is correlated with poor prognosis.[104]

In the healthy periodontium, keratinocytes protect the oral and sulcular epithelium by producing hBDs. In addition, neutrophils protect the junctional epithelium by secreting defensins.[9] Neutrophils are short-lived cells and aged neutrophils undergo apoptosis. However, in inflamed periodontal tissues, apoptosis of neutrophils can be delayed.[105] A local homeostatic mechanism protects the periodontal tissue against the destructive potential of recruited inflammatory cells. One of these regulating mechanisms may be developmental endothelial locus-1 (Del-1). In embryonic development stages, Del-1 promotes embryonic vascular development. Del-1 is a ligand for lymphocyte function-associated antigen 1 (LFA-1). The adhesive interactions between LFA-1 on neutrophils and intercellular adhesion molecule 1 (ICAM-1) on endothelial cells promote the adhesion of neutrophils onto the vascular endothelium and extravasation of neutrophils.[106] The neutrophil transmigration is an important event in immunity.[107] In acute phase of inflammation, IL-17 enhances neutrophil influx to sites of inflammation.[108] Neutrophils produce MMP-8 which has a great impact on the degradation of connective tissue in periodontal tissues.[109] In periodontitis, neutrophil functions as a double-edged sword. While it is essential for host defense, it enhances periodontal tissue breakdown by producing lytic and proteolytic enzymes.[110] *P. gingivalis* inhibits the synthesis of E-selectin, IL-8 (also known as CXCL8) and ICAM-1 to decrease neutrophil recruitment.[105] In cancers, neutrophils display both anti- and pro-tumor properties as they are able to kill tumor cells and regulate tumor growth and metastasis via pro-angiogenic factors.[104] Very recent study has found a possible association between periodontitis and total leukocytes counts, neutrophil counts and hematocrit (HCT) levels.[111]

In healthy gingiva, CD4+ helper T cells are the most dominant T lymphocytes. These cells have important roles in the adaptive immune responses. CD8+ T cells are the second most abundant T lymphocytes in healthy gingiva. Under homeostatic conditions these cells can down-regulate the inflammatory responses. Therefore, they maintain gingival tissue integrity and suppress osteoclastogenesis.[112] T helper cells such as Th1, Th2, Th9, Th17 and Th22 contribute to cell-mediated immune responses by producing different pro-inflammatory cytokines such as IL-1, IL-17E and IL-17 which activate other immune cells such as neutrophils and B cells. Activation of both T cells and B cells results in the production of RANKL which causes alveolar bone resorption by osteoclasts.[112] Besides, memory B cells have been detected in the apical connective tissue of healthy gingiva. B cells contribute to gingival homeostasis and inflammatory responses by producing antibodies against periodontal pathogens.[113] A growing body of evidence shows that B cells contribute to tumor promoting microenvironment through secretion of IL-10.[114] A previously published study has shown the increased number of $CD86^+$ B cells in the tumor microenvironment of head and neck SCC compared to normal mucosa.[115]

Tregs $CD4^+$ T lymphocytes play a critical role in the maintenance of self-tolerance and immune homeostasis. Tregs suppress the naïve T cell activation and expansion. During periodontitis, Tregs accumulate at inflamed tissues to limit the immune responses and promoting pathogen survival by secreting cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), Glucocorticoid-induced tumour necrosis factor receptor-related protein (GITR), CD103, CD45RO, and Foxp3.[116] The role of regulatory CD4 T cells (Tregs) in cancers is controversial. Although some studies have observed a poor prognosis associated with increased number of Tregs, some other studies have reported a better prognosis.[117,118]

Involvement of some other cytokines and chemokines in periodontitis and oral cancer

Cytokines is classified as pro-inflammatory and anti-inflammatory groups. Any imbalances between their relative concentrations may result in tissue destruction. Chemokines recruit leukocytes and other immunological mediators in periodontal inflammatory foci. Besides, chemokines and their receptors are involved in the cell proliferation, cell motility, angiogenesis, cancer development and metastasis.[120] In the oral cavity, different cell types synthesize chemokines including neutrophils, lymphocytes, monocytes/macrophages, fibroblasts, osteoblasts, endothelial cells, epithelial cells and mast cells.[120] For example, gingival epithelium produces some cytokines such as IL-1, IL-8, and TNF-*α* which in turn can recruit the macrophages.[113] Pro-inflammatory interleukins such as IL-1 and IL-6 promote the secretion of hBDs from keratinocytes.[8,121] Additionally, IL-6 plays a crucial role in the development of periodontitis through a crosstalk of fibroblasts and macrophages.[122] C-X-C motif chemokine 5 (CXCL5), a pro-inflammatory and pro-angiogenic chemokine, has been indicated in the serum of smokers with periodontitis.[123] C-X-C motif chemokine receptor 2 (CXCR2), expressed on the surface of neutrophils, plays a crucial role in the recruitment of neutrophils.[124] CXCL10 has been indicated in inflamed gingival tissues in response to interferon-γ, TNF-α, and IL-1β.[120,125] One of the most abundant chemokines in the oral cavity is IL-8 (CXCL8) which can be found in both healthy individuals and patients with periodontitis. Besides, CXCL12 enhances the activity of MMP-9 in osteoclasts to promote bone resorption.[120] TNF-α, IL-1β regulate osteoclastogenesis and induce bone resorption via enhanced expression of receptor activator of NF-kB ligand (RANKL).[126,127] A previous animal study demonstrated that IL-17A promotes alveolar bone loss in a *P. gingivalis* induced model of periodontitis by activating NF-Kβ. In addition, IL-17A collaborates with TNF-α and IL-1β to enhance the expression of pro-inflammatory media-

tors by keratinocytes and fibroblasts.[128] Furthermore, overexpression of some other chemokines such as CXCL10 promotes tumor associated inflammation.[70] IL-8 and CXCR2 have been detected in OSCC.[129] CXCL5, a chemotactic for neutrophils, drives oral cancer cell growth.[120]

Table 4[70,120,125,130-139] lists some cytokines and the signaling pathways involved in periodontitis and oral cancer.

The role of autophagy in periodontitis and oral cancer

Autophagy, an intracellular catabolic process, has a great impact on cellular homeostasis via the elimination of the damaged organelles and aggregated intracellular proteins. Autophagy process starts with the formation of autophagosomes which capture degraded components and later they fuse with lysosomes to recycle those components.[140] Autophagy plays an essential role in inflammation, autoimmunity and cellular differentiation.[141] Compared with healthy periodontal status, a higher level of autophagy activity has been found in periodontitis. It has been suggested that autophagy protects periodontal cells from apoptosis, promotes angiogenesis and facilitates oral bacteria to escape from the host's responses.[142] Oral bacteria invade the gingival epithelium by controlling the autophagy process. For example, *P. gingivalis* promotes its own survival and invasion of periodontal tissues by employing the autophagy processes.[92] On the other hand, autophagy process is upregulated in many cancer types including head and neck cancer.[143] In many cancers, autophagy has dual roles in tumor suppression and promotion. According to the recent study, oral cancer cells promote macro autophagy as an adaptive mechanism to invasion of *P. gingivalis*. This mechanism can limit the bacterial toxicity and help cancer cells to survive.[92] Besides, autophagy modulates the characteristics of cancer stem cells.[140]

Genetic alterations and the risk of periodontitis development and carcinogenesis

Several genetic disorders affect periodontal tissues. While some disorders alter the host immune response to periodontal infections, some others cause defects in the gingiva or periodontal connective tissue.[144,145] Severe periodontitis have been recorded in Down syndrome (trisomy 21), Chediak-Higashi syndrome and Papillon-Lefèvre syndrome.[145] Congenital neutropenia is associated with oral ulcerations and periodontitis.[144] A previously published systematic review showed that polymorphisms in the IL-1α, IL-1β, IL-6, IL-10, MMP-3, and MMP-9 genes are significantly associated with an increased risk of development of periodontitis.[146] Also, increased expression of the human telomerase reverse transcription (hTERT) enzyme has been noticed in patients with periodontitis.[147,148] Carcinogenesis is a multi-step process. Genetic alterations and different signaling pathways result in cell proliferation, resistance to apoptosis, invasion and metastasis.[149] In the oral cavity, prolonged exposure to carcinogens results in the molecular alterations in the epithelium which lead to the formation of a pre-neoplastic (pre-cancerous) lesion.[14] Overtime, this pre-neoplastic field develops to multiple cancers.[14] A previously published work on the expression profile of hTERT has found a steadily increased expression level of hTERT from normal oral mucosa to oral epithelial dysplasia to OSCC.[150] Another published paper has revealed that the earliest cytogenetic alterations in both non-smokers and smokers are loss of heterozygosity (LOH) and loss of tumor suppressor genes in the oral epithelium.[151] Chromosal instability detection could be a reliable technique for a risk assessment of oral pre-malignancies and may contribute to an appropriate treatment regimen.[152]

Role of microRNAs in the etiopathogenesis of periodontal disease and oral cancer

Altered expression of microRNAs contributes to many cellular immune responses.

Dysregulation of miRNA expression has been reported in biofluids such as serum, saliva and crevicular fluid of the gingiva.[17,153,154] The role of miRNAs in pathobiology of periodontal diseases and oral cancer has been demonstrated. For example, miR-1226-5p is down regulated in patients with periodontal diseases and it has been suggested that this miRNA could be a biomarker of periodontitis.[155] Moreover, miR-21 expression is up-regulated in *P. gingivalis* lipopolysaccharide (LPS) stimulated macrophages; therefore, miR-21 could be a target for the control of periodontitis. MiR-21 deficiency increases the synthesis of pro-inflammatory cytokines and promotes activation of NF-κB in *P. gingivalis* LPS - stimulated cells.[156] Also, the expression level of miRNA-146 was increased in human gingival fibroblasts after *P. gingivalis* LPS stimulation. This finding indicated that miRNA-146 inhibits pro-inflammatory cytokine secretion via regulating IL-1 receptor-associated kinase 1(IRAK1), IL-1β, IL-6 and TNF-α production.[157]

Elevated expression of miR-143-3p was demonstrated in periodontitis. K-RAS is the target gene for miR-143-3p.[158] Up-regulation of miR-15a, miR-29b, miR-125a, miR-146a, miR-148/148a,

Table 4. List of some cytokines and the signaling pathways involved in periodontitis and oral cancer.

Type of cytokine (reference no.)	Mechanism/signaling pathway
IL-6 (70,130-133)	Classic (specific membrane-bound IL-6 receptor) and trans-signaling (sIL-6R), TLR, NF-κB/ ERK1/2, PI3K/AKT/NF-κB, STAT1
IL-1β (130,134)	Induction of IL-6 and osteoclastogenesis-mediated bone loss by targeting osteoclasts
IL-8 (132,133)	NF-κB/ ERK1/2, PI3K/AKT/NF-κB
TNF-α (135,136)	TNF-α/HIF-1α/VEGF, RANK and RANKL
IL-17A (137)	TLR
CXCL5 (138,139)	Increasing the number of neutrophils, AKT/NF-κB
CXCL12 (120)	Activation of MMP-9
CXCL10 (125)	RANKL, osteoclastogenesis

miR-223, and down-regulation of miR-92 have been noticed in patients with periodontitis.[4] Furthermore, down-regulation of miR-100, miR-125b and up-regulation of miR-Let-7a and miR-21 have been reported in periodontitis. NFκB is the common target for aforementioned miRNAs.[159] Neutrophils express some miRNAs in periodontitis. In a mouse periodontitis model, up-regulation of miR-155, and miR-223 and down-regulation of miR-17 and miR-31 in neutrophils has been noticed.[4] IL-8 was a target of miR-155 and *CXCL2*, C–C motif chemokine 3 (*CCL3*) and IL-6 were the main targets of miR-223. ICAM-1 and E-selectin expression were detected as the potential targets of miR-31 and miR-17-3p, respectively.[4] On the other hand, elevated expression of miR-21, miR-181b, and miR-345 is associated with malignant transformation of oral leukoplakia.[153] Additionally, upregulation of miR-31 is negatively associated with oral leukoplakia progression.[17,160] Altered expression of several miRNAs has also been recorded in oral cancer. For example, down-regulation of miR-143 and miR-145 and miR-590 has been reported in oral cancer cells.[161] Decreased expression level of miR-100 and miR-125b elevates oral cancer cells proliferation.[162] Detailed information about the miRNAs involved in periodontitis and potential targets is presented in Table 5.[4,155-158]

Figure 1 summarizes the involved factors in chronic periodontitis which promote the oral cancer development.

Salivary proteins can be used as biomarkers of periodontitis and oral cancer

Many studies have attempted to find potential biomarkers in the periodontitis. For instance, salivary matrix metalloproteinase-8 (MMP8) is higher in patients with periodontitis and can be used as a biomarker for periodontitis.[163] Recently, higher concentrations of CXCL10 have been identified in the saliva of patients with chronic periodontitis and severe bone loss.[125] Some other salivary biomarkers in periodontitis are IL-1β, MMP9,[164] mucin 4 (MUC4) and matrix metalloproteinase 7 (MMP7).[165] MMP-8 (or collagenase 2) which is found in oral fluid of patients with periodontitis can be considered as one of the most promising biomarkers.[166] Salivary extracellular vesicles (EVs) can be used as non-invasive sources of different miRNAs for OSCC diagnosis.[167] Also, altered concentrations of choline, betaine, pipecolinic acid and l-carnitine can help in the early detection of OSCC.[168]

Some similarities and differences between periodontal diseases and oral squamous cells cancer

Clinically, advanced periodontitis and oral cancer, especially gingival cancer, share some signs and symptoms such as swelling, bleeding, deep periodontal pockets, bone destruction and tooth mobility.[4,169] However, there are some differences which can help to differentiate gingival SCC from periodontal diseases: i) periodontal diseases are not stable and respond to therapies; ii) unlike gingival SCC, periodontal diseases are more generalized; iii) in both diseases, bone loss and widening of periodontal ligament space occur but in gingival SCC more aggressive pattern of bone

Table 5. The detail of miRNAs involved in periodontitis and potential targets.

Involved miRNAs (reference no.)	Potential targets
ImiR-1226-5p (155)	Not mentioned
miR-21 (156)	NF-κB
miRNA-146 (157)	IRAK1, IL-1β, IL-6 and TNF-α
miR-143-3p (158)	K-RAS
miR-15a, miR-29b, miR-125a, miR-146a, miR-148/148a, miR-223, miR-92, miR-100, miR-125b, miR-Let-7a and miR-21 (4)	NFκB
miR-155 (4)	IL-8
miR-223 (4)	CXCL2, CCL3 and IL-6
miR-31 (4)	ICAM-1
miR-17-3p (4)	E-selectin

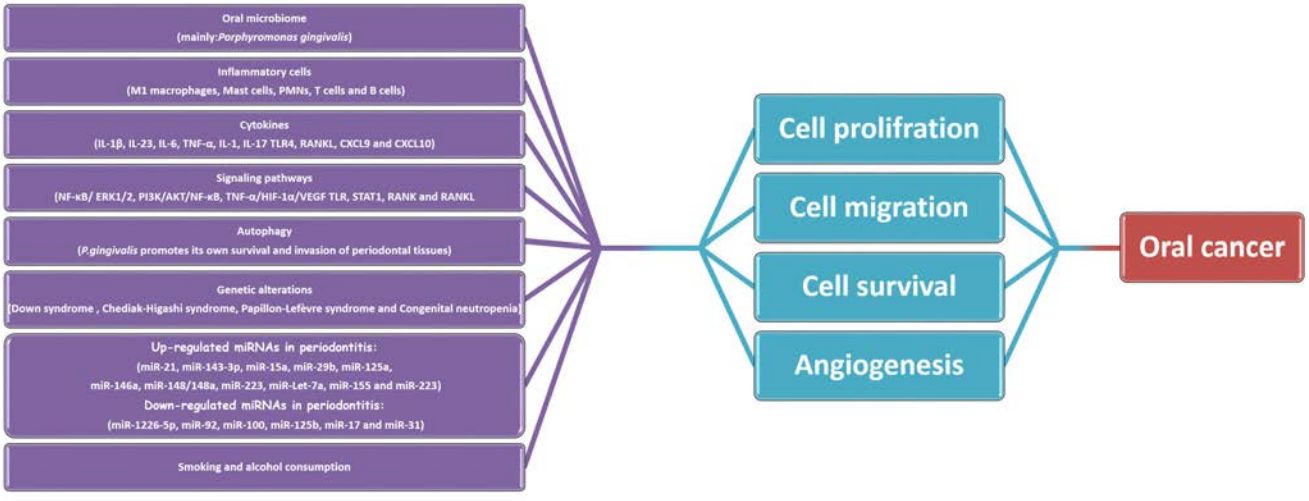

Figure 1. Overview of the major mechanisms that chronic periodontitis promotes oral cancer. Oral microbiome induces inflammation, chemokine production and autophagy which enhance genetic alterations. In addition, some miRNAs, smoking and alcohol consumption are involved in cell proliferation, cell migration, cell survival and angiogenesis which play essential roles in oral cancer development.

destruction can be noticed. However, in both cancer lesions and periodontal diseases, severe bone resorption and tooth mobility can be seen.[170]

Treatment protocols for periodontitis and oral cancer

The primary treatment for oral cancer patients is surgery. Despite the development of effective drugs for some cancers, there is no effective chemotherapeutic agent for OSCC.[171] Unfortunately, no established role of adjuvant chemotherapy has been identified for oral cancer. Most chemotherapeutic drugs utilized for oral cancer treatment, only decrease the tumor size before surgery.[171] Adjuvant chemotherapy after surgery may reduce the incidence of recurrence and metastasis. In addition, adjuvant chemotherapy may reduce radiation resistance. Cisplatin is associated with an increased risk for acute and late toxicities. Cetuximab combined with radiation has been studied for the primary treatment of locally advanced unresectable head and neck cancer but the role of Cetuximab is not recommended for oral cancer patients.[172] Recent studies indicate that inflammatory mediators have a great impact on the development of resistance to chemotherapeutic agents and tumor progression. Thus, cancer cells which are continuously exposed to inflammatory signals acquire chemoresistance and more aggressive behaviors. Therefore, it can be concluded that infection of cancer cells with oral microbiome is the main cause of chemoresistance in the oral cavity.[171] As both periodontitis and oral cancer are common in adults, thus, periodontitis-related pathogens and mediators are considered as the main cause of chemoresistance of cancer cells.[171] According to the recent investigation, inflammatory mediators especially IL-6 provoke resistance to paclitaxel.[171] Interestingly, the prophylactic administration of ibuprofen improves the resistance of OSCC to paclitaxel.[171] For that reason, it is logical to treat periodontitis as an inflammatory lesion and a promoter of cancers. Therapeutic protocol includes improvement of individual oral-hygiene, smoking-cessation, dietary adjustment, subgingival scaling, local and systemic pharmacotherapy; and different types of surgery.[173]

Discussion and Conclusions

Periodontitis is an inflammatory response to oral microbiotome and is associated with bone loss and tooth loss.[10] Exposure to inflammatory conditions promotes the infiltration of immune cells to the oral mucosa. Inflammation and immune related mediators have been accepted as the hallmarks of malignant transformation.[70] There are some reports about the association between periodontitis and different cancers such as breast cancer and head and neck cancer.[59,174] *P. gingivalis* is the main cause of periodontitis. Due to genetic alterations in response to chronic infection *P. gingivalis* could contribute to malignant transformation.[88] Several life style factors, including poor oral hygiene, poor nutrition, alcohol consumption, cigarette smoking and obesity are important risk factors for both periodontitis and oral cancer.[175-177] Also, genetic alterations have been considered to be involved in periodontitis and oral cancer.[20] The recent genetic and molecular studies can explain the high risk of development of cancers from pre-existing inflammatory lesions such as periodontitis. Due to high prevalance of periodontitis and the risk of developing of different cancers including oral cancer around the world, diagnostic and therapeutic strategies for periodontal treatment need to be considered. Similarities in clinical presentations among patients with periodontitis and oral cancer encourage the clinicians to find more reliable and non-aggressive tools for early detection of oral cancer. Early detection of oral cancer has a great impact on the patient prognosis and salivary biomarkers and chemokines are the most promising tools for the early detection of oral cancer.

In conclusion, periodontitis is a common disease around the world. Oral microbiome is the main causative factor for periodontal diseases. Inflammatory responses can increase the risk of genetic alterations and malignant transformation. Oral cancer is a multistep process which involves many signaling pathways. Understanding the signaling pathways and using biomarkers can help to the early detection of oral cancer. Doctors should consider that patients with periodontitis have been linked to an increased risk of oral cancer. Education and training of oral health practitioners can reduce the consequences of both periodontitis and oral cancer.[178]

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