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Review Article

Links demystified: Periodontitis and cancer

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ABSTRACT

Cancer is marked by the uncontrolled growth of cells, tissue invasion and metastasis to various organs via the circulatory and lymphatic systems. Recent data have expanded the concept that inflammation is a critical component of tumor progression. Many cancers arise from sites of infection, chronic irritation, and inflammation. The tumor microenvironment, which is largely orchestrated by inflammatory cells, is an indispensable participant in the neoplastic process, fostering proliferation, survival, and migration. Periodontal disease, a chronic inflammatory condition is characterized by an oral bacterial infection leading to inflammation within the supporting tissues of the teeth, which often leads to the destruction of the periodontal tissues and alveolar bone that support the teeth. This oral inflammation often has systemic effects leading to an increased concentration of circulating inflammatory markers with the severity of disease being correlated directly with levels of serum inflammatory markers. Periodontal infection has been linked to organ and systemic diseases. There is documented evidence of significant associations between cancer of the lung, kidney, pancreas, hematological and oral cancers, and periodontal disease. This articles reviews and summarizes the possible biological mechanisms involved between periodontal infection and cancer.

Key Words: Cancer, periodontitis, plausible mechanisms

INTRODUCTION

Cancer, as a heterogeneous group of disorders with marked different biologic properties, is thought to arise from a single cell, where series of genetic alterations in tumor-suppressor genes and oncogenes are responsible for continued clonal selection and tumor cell heterogeneity, resulting in tumor proliferation, invasion, metastasis, and drug resistance.[1] Cancer accounts for a large group of diseases with high morbidity. Cancer has been identified as the most common cause of death in the age group below 65 and the second most common in the age group above 65. It is also the cause of over 20% of the mortality rate in human societies.[2]

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Nearly all cancers are caused by abnormalities of the genetic material of the transformed cells.[3] Cancers are classified by the primary type of tissue from which they originate, and prognosis is determined by the type of cancer and the stage or the extent of disease.[4] The six hallmarks that classically characterize cancer include self-sufficiency in growth signals, evading apoptosis, insensitivity to antigrowth signals, sustained angiogenesis, limitless replicative potential, tissue invasion, and metastasis. Cancer related inflammation is considered as the seventh hallmark of cancer.[5] Inflammation can play a role in tumor suppression by stimulating an antitumor immune response, but more often, under certain conditions, it appears to stimulate tumor development.[6] The intensity and nature of the inflammation could explain this apparent contradiction.[7]

Periodontitis is chronic and inflammatory. Periodontal infection has been linked to organ and systemic diseases, such as cardiovascular disease, diabetes mellitus, and adverse pregnancy outcomes. What is unknown is the link or the possible link between

periodontal disease and cancer. Hence, this review addresses common ground for progression of periodontal disease and cancer based on inflammatory mechanisms that could fuel progression.

INFLAMMATION AND CANCER

Inflammation is a physiological process crucial for the function of the innate immune system as it is a response to acute tissue damage.[6] The immune system reacts to harmful stimuli by a hyper-inflammatory response. Recently, it has been suggested that inflammation associated with cancer is similar to that seen with the chronic inflammation.[8] The German Pathologist Virchow is credited with suggesting the causal link between inflammation and cancer in the 19th century.[9]

The interlink between inflammation and cancer can be thought of as consisting of two pathways: An extrinsic mechanism, where a constant inflammatory state contributes to increased cancer risk; and an intrinsic mechanism, where acquired genetic alterations trigger tumor development.[10,11] The roles and the relationship between the two pathways in the cancer development process depend on their specific interactions between genetic/epigenetic factors and environmental factors.[12-14]

Inflammation is present in cancer tissues that arose without precancerous inflammation. The smoldering inflammatory state is necessary to maintain and promote cancer progression and accomplish the full malignant phenotype, such as tumor tissue remodeling, angiogenesis, metastasis and the suppression of the innate anticancer immune response and alters responses to hormones, and chemotherapeutic agents.[15] In these cancers, inflammation is elicited by genetic and/or epigenetic mutation that triggers cell transformation and maintains the autonomous proliferation of the transformed cells.

PERIODONTITIS

Periodontitis is a chronic inflammatory disease of the supporting structures of the teeth initiated by pathogenic bacteria.[16,17] Periodontal disease progression is signaled by a shift in the bacterial makeup of the dental biofilm from largely aerobic Gram-positive bacteria to a pathogenic infectious state dominated by anaerobic Gram-negative organisms.[18-20] Thus, the onset of periodontal disease is marked by a shift in the dominant strains composing the dental biofilm.[21,22]

Periodontal disease may contribute to the establishment of a systemic inflammatory condition in genetically susceptible individuals known as "hyper-inflammatory phenotype," potentially involving increased production of inflammatory mediators and a breakdown of pathways responsible for the immune resolution.[20,23] Research suggests that the ongoing inflammatory response instigated by periodontal pathogens leads to an increase in numerous markers of systemic inflammation including C-reactive protein, Interluekin [IL]-1 β, IL-6,Tumor Necrosis Factor [TNF]-α, proteases including Matrix metalloprotenases (MMP), Prostanoids, and acute phase proteins.[20,24-26]

Recent epidemiologic research has linked periodontal pathogens to several systemic diseases, including cardiovascular disease, diabetes mellitus, preterm birth, respiratory disease, osteoporosis possibly mediated through markers of systemic infection, and inflammation.[20,27-30] The results of several epidemiologic studies have also suggested a possible positive association between periodontal disease and cancer risk in the different tissues.[31-37]

Mechanisms of carcinogenesis could also differ by site. For example, bacteria may play a more direct role in carcinogenesis in the mouth or lung, whereas in more distant organs, systemic inflammation or nitrosamines, reactive oxygen species (ROS) may play a more important role.

Different plausible explanations linking Periodontitis and cancer include:[38]

1. Chronic inflammation induced by periodontal pathogens serves to promote already initiated cells, leading to the breakdown of normal cell growth control, and potential carcinogenesis.
2. Periodontal bacteria may also play a more direct role through local inflammatory responses and carcinogenic transformations. *Helicobacter pylori* infection is a well-characterized example.
3. Chronic periodontal disease may indicate that an individual's immune system is deficient at clearing infection, and subsequently deficient at surveillance for tumor growth.
4. Increased cancer risk is attributed to the observation that chronic periodontal inflammation can cause genetic damage via production of oxidizing compounds, such as reactive oxygen and nitrogen species.
5. Wound healing and carcinogenesis have several biological processes in common and carcinogenesis

may be considered to be a mis-regulated form of wound healing.
6. Failures of mechanisms required for resolving the periodontal inflammatory response.

Inflammatory loading

Role of inflammatory cells

Mechanisms associated with systemic inflammatory burden and increased levels of carcinogenic compounds generated in response to periodontal pathogens and sequelae of inflammatory mechanisms, could contribute to the development of cancer. Inflammatory cells are co-opted into the neoplastic process.

Inflammatory cells have powerful effects on tumor development. Early in the neoplastic process, these cells are powerful tumor promoters, producing an attractive environment for tumor growth, facilitating genomic instability and promoting angiogenesis. Later in the tumorigenic process, neoplastic cells divert inflammatory mechanisms to favor neoplastic spread and metastasis.

Although inflammatory responses should be anti-tumor, cancer patients are often defective in their inflammatory responses. This may arise by two distinct tumor-mediated mechanisms: A failure to upregulate the anti-inflammatory cytokines, or subversion of the host response resulting from desensitization of receptors owing to high chemokine and cytokine concentrations that then blunt systemic responses.

In periodontitis induction of an immune response begins when an antigen penetrates epithelial surfaces. Antigen will eventually come into contact with macrophages or certain other classes of antigen presenting cells, which include B cells, monocytes, dendritic cells, Langerhans cells.

Monocytes, in the presence of granulocyte-macrophage colony-stimulating factor (CSF) and IL-4, differentiate into immature dendritic cells.[39] Dendritic cells migrate into inflamed peripheral tissue where they capture antigens and after maturation, migrate to lymph nodes to stimulate T-lymphocyte activation. Soluble factors such as IL-6 and CSF-1, derived from neoplastic cells, push myeloid precursors toward a macrophage-like phenotype.[40]

Tumor Associated Macrophages (TAM) influence fundamental aspects of tumor biology. TAMs have a dual role in neoplasms — although they may kill neoplastic cells,[41,42] they also produce mediators that potentiate neoplastic progression.[43] The pro-tumor functions of TAM is to promote the survival of neoplastic cells from apoptotic stimuli, proliferation, and tumor angiogenesis. TAM have an intense proteolytic activity and degrade the extracellular matrix (ECM), favoring tumor cell intra-vasation and dissemination to distant sites.[13]

Macrophages are not unique among inflammatory cells in potentiation of neoplastic processes. Genetic and functional experiments indicate that neutrophils, mast cells, eosinophils and activated T lymphocytes also contribute to malignancies by releasing extracellular proteases, pro-angiogenic factors and chemokines.[44-46]

Role of soluble mediators in cancer related inflammation

Chronic inflammation affecting the periodontium results in the release of a steady stream of cytokines, prostaglandins, bacterial toxins, and enzymes from the host and bacterial cells, which have a damaging effect on the periodontium. Furthermore, periodontal pathogens and inflammatory mediators travel with the saliva and blood from the affected tissues to distant sites and adversely affect systemic health.

The primary inflammatory cytokine TNF, produced not only by immune cells, but also by malignant and stromal cells, is an activating mediator and at low concentrations sustains the growth of tumor cells and blood vessels. The mechanism of TNF-α action includes direct effects on tumor spread, via chemokine receptor 4 (CXCR4); tumor cell survival, stimulation of new blood vessels due to induction of CXCL12 andVascular Endothelial Growth Factor VEGF, increased release of chemokines (CXCL8, CXCL 12) and activation of matrix degrading enzymes.[47]

IL-1, IL-6, TNF-α, and the related receptor activator of Nuclear Factor kB [NF κB] ligand have long been known to augment the capacity to metastatize by affecting multiple steps in the dissemination and inflammation cascade.[13]

IL-6 is a key growth-regulating and anti-apoptotic cytokine, having tumor-inducing activities by promoting proliferation of both malignant and stromal cells. These actions are mediated by gp130 and Signal Transducer and Activator of Transcription (STAT)3.[48] In tumor cells, STAT3 induces the expression of genes important for cell cycle progression (such as cyclin D and proliferating cell nuclear antigen) and suppression of apoptosis.[49]

IL-1 promotes tumor growth and metastasis by inducing several pro-metastatic genes such as metalloproteinases, chemokines, growth factors, and Transforming Growth Factor (TGF)β.[50] IL-1 is a potent proangiogenic cytokine and VEGF release is also IL-1 dependent.[51,52]

Chemokines, another soluble components are key players in cancer-related inflammation, and TAM are a rich source of different inflammatory chemokines.[53] Chemokines were initially defined functionally as factors regulating directional migration of leukocytes during states of inflammation; however, chemokine biology extends to all cell types, including the most human neoplastic cells.[54]

A variety of chemokines, including CCL2, CXCL12, CXCL8, CXCL1, CXCL13, CCL5, CCL17, and CCL22, have been detected in neoplastic tissues as products of either tumor cells or stromal elements.[55] CXCL1 and related molecules (CXCL2, CXCL3, CXCL8, or IL-8) have an important role in tumor progression by stimulating neoplastic growth, promoting inflammation, and inducing angiogenesis. Strong evidence demonstrates that levels of CCL2 play an important role in the regulation of angiogenesis.[9]

Periodontal pathogens: Role of *H. Pylori*

H. pylori gastric infections are prevalent universally and could contribute to serious medical problems, ranging from gastritis and its sequelae to gastric carcinoma or lymphoma.[56,57] *H. pylori* have also been isolated from the subgingival biofilm of subjects with chronic periodontitis and poor oral hygiene,[58-60] suggestive of colonization by this species when periodontal pocketing and inflammation are present. Failure to eliminate the species from oral niches could lead to recolonization and reinfection in the gastric mucosa.

Progressive chronic inflammation and the diversity of periodontal pathogens could provide a range of nutrients and binding sites for *H. pylori*. *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*.[61] An urea rich subgingival environment is likely to be selective for *H. pylori*, being a urease producing microorganism.

The association between subgingival biofilm, severe periodontal disease and *H. pylori* infection is a pertinent one with regard to the possible influence of periodontal status on gastric mucosal inflammation and carcinogenesis. The role of *H. pylori* infection in the progressive cyto-histological differentiation associated with gastric carcinoma has been established; along pathways leading to production of ROS and oxidative damage to DNA in combination exogenous and endogenous factors.[62] The induction of a systemic MMP response was demonstrated in response to *H. pylori* with the release of MMP-8 and other poly morphonuclear neutrophils degranulation products.[63] This reflects accelerated proteolysis and oxidative stress with possible extra-intestinal sequelae affecting oxidative stress driven diseases.

wound healing and carcinogenesis-the link

In response to tissue injury, multifactorial network of chemical signals initiate and maintain a host response designed to "heal" the afflicted tissue.

Wound healing and carcinogenesis have several biological processes in common and carcinogenesis may be considered to be a mis-regulated form of wound healing. The key concept is that normal inflammation is usually self-limiting; however, dysregulation of any of the converging factors can lead to abnormalities and ultimately, pathogenesis.[64,65]

Integrins comprise a large family of transmembrane receptors that mediate adhesion in the cell substratum. The epithelium-specific integrin, αvβ6 is a receptor for the ECM proteins.[66]

Integrin αvβ6 is present in healthy junctional epithelium and down-regulated in human periodontal disease. Integrin αvβ6 knockout mice developed severe chronic periodontal disease.[67] This integrin, appears to play a central role in preventing the initiation of periodontitis.[67]

The integrin αvβ6 is up-regulated in cancer, with the possible progression of carcinogenesis, and during wound healing.[67] Functions of increased expression of αvβ6 integrin include promotion of cell migration, control of cell proliferation, activation of TGF-β1, mediation of cancer cell invasion, suppression of apoptosis and modulation of matrix metallo proteinases activity. It is difficult to speculate on which of these is active when αvβ6 is up-regulated *in vivo*.[67]

Resolution of inflammation

Resolution of inflammation is an important aspect of homeostasis in inflammatory diseases such as periodontal disease and cancer progression. Stereoselective chemical

mediators referred to as resolvins (Rvs), protectins and lipoxins (LXs) control the duration and magnitude of inflammation; and signal resolution. In view of their potent actions in human disease models, their deficiency could lead to inadequate resolution pathways and escalation of diseases.[68,69]

These mediators are an important consideration in the resolution of inflammation, especially in chronic disorders like Periodontitis where the inflammatory loading from chronic inflammation could lead to carcinogenesis. They appear to be potent regulators of leukocytes and the production of cytokines, leading to the regulation of inflammatory sequelae and resolution relevant to carcinogenesis. Rvs are synthesized from omega-3 fatty acids eicosapentanoic acid and docosahexaenoic acid via cyclooxygenase-2/lipooxygenase (COX-2/LOX) pathways. LXs are also formed from COX-2/LOX pathways. Anti-tumorigenic effects have been demonstrated for metabolites of 15-LOX-1 and 2; and the COX-2 acetylation product 15-epi-Lipoxin [LXA4] in response to low dose aspirin. When non-steroidal anti-inflammatory drugs like aspirin are acetylated, the mechanism for forming Prostaglandin [PG]E2 from COX-2, which promotes tumorigenesis, switches to the synthesis of 15-epi-LXA4, which ameliorates this effect due to anti-tumorigenesis.[70] Considering the interconnected pathways of pro-inflammatory mediators and cytokines, the anti-inflammatory properties of pro-resolving mediators need further investigation in the context of preventing carcinogenesis in response to over-exuberant inflammatory responses, which may be linked to chronic periodontitis.

Role of reactive oxygen and nitrogen species

Increased cancer risk is attributed to the observation that chronic inflammation can cause genetic damage via production of oxidizing compounds, such as reactive oxygen and nitrogen species.

Leukocytes and other phagocytic cells induce DNA damage in proliferating cells, through their generation of reactive oxygen and nitrogen species that are produced normally by these cells to fight infection.[71] Endogenous nitrosamines formation in the oral cavity are stimulated by nitrate-reducing bacteria, promoted by poor oral hygiene and periodontal disease as well as by tobacco use and certain dietary factors.[72,73] Tooth loss resulting from poor oral hygiene may also contribute to greater nitrosamine production.[74]

These species react to form peroxynitrite, a mutagenic agent. Hence, repeated tissue damage and regeneration of tissue, in the presence of highly reactive nitrogen and oxygen species released from inflammatory cells, interacts with DNA in proliferating epithelium resulting in permanent genomic alterations such as point mutations, deletions, or rearrangements. Indeed, p53 mutations are seen at frequencies similar to those in tumors in chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease.[75]

Association between periodontitis and cancer

There are many hypotheses for the possible association between periodontal disease and cancer, total and by site [Table 1].

Although these studies have been conducted in different populations and have used different measures of periodontal status, associations with oral, gastric and pancreatic cancers tend to persist despite tight control for smoking.

CONCLUSION

It is relevant that chronic periodontitis is associated with a small, but significant overall cancer risk, which persists in non-smokers. Further research is warranted to confirm many of the positive associations between periodontal disease and various cancers. As the role of periodontal disease in the etiology of cancers is further elucidated, possible biologic mechanisms can be explored. Periodontal disease may be a sign of a deficiency of the overall immune system or it may have a direct cause of cancer. Periodontal disease may also be a useful marker of a susceptible immune system, or directly affect cancer risk as a result of inflammatory loading. The size of the inflammatory burden based on disease aggression and distribution of Periodontitis have implications on the impact factor. The future challenge is to determine the nature of the link — causal or casual. Finally, there is some advantage in oncologists working with the dental specialists in cases of cancer of the oral cavity. It would be relevant to categorize periodontal disease at the time of cancer diagnosis. This poses interesting dimensions for medical oncologists being familiar with periodontal diagnosis in terms of disease aggression at the time of diagnosis and cancer outcome with varying aggression of periodontal diseases. Patient care could be improved with close liaison between oncologists and periodontists.

Table 1: Various associations between periodontal disease and cancer

Pancreatic cancer and periodontitis	
Stolzenberg-Solomon *et al*.[32]	Tooth loss was associated positively with pancreatic cancer but not significantly associated with *H. pylori* seropositivity
Hujoel *et al*.[33]	Individuals with periodontitis have an elevated risk of death from cancer and there is a suggestion of an association with Pancreatic cancer. Adjustment of potential confounders reduced this association
Michaud *et al*.[31]	When compared to no history of periodontal disease, there is an increased pancreatic cancer risk in those with a self-reported history of periodontal disease
Lung cancer and periodontitis	
Hujoel *et al*.[33]	Periodontitis was associated significantly with total cancer death, but lung cancer specifically. However, the biological plausibility may be remote and more studies are needed in a population in which smoking prevalence is lower
Tu *et al*.[76]	No association was found between tooth loss and lung cancer both with and without adjustment for baseline smoking status
Gastrointestinal cancer and periodontitis	
Watabe *et al*.[77]	A significant dose-response relationship was observed between the odds of developing gastric cancer and the number of teeth loss
Abnet *et al*.[34]	A significantly elevated risk of esophageal squamous cell carcinoma, Gastric cardia adenocarcinoma, and gastric non-cardia adenocarcinoma was found to be strongly associated with the loss of teeth
Abnet *et al*.[35]	A significant relationship was found between tooth loss and risk of dying from upper gastrointestinal cancer with age as an effect modifier
Abnet *et al*.[74]	Edentulous patients had a significant two fold increase in the risk of gastric non-cardia adenocarcinoma compared with those with <10 teeth. No statistically significant associations were found between tooth loss and esophageal squamous cell carcinoma or esophageal gastric adenocarcinoma
Oral cancer risk and periodontitis	
Zheng *et al*.[78]	After adjustment for tobacco smoking and alcohol consumption missing teeth emerged as a strong risk factor for oral cancers
Marshall *et al*.[79]	Poor oral hygiene increased risk of oral cancers; however, the risk is smaller than that of cigarette and alcohol use
Bundgaard *et al*.[80]	A two fold increase in intraoral squamous cell carcinoma was found in patients with less than five teeth compared with patients with 15 or more teeth after correcting for tobacco and alcohol consumption
Talamani *et al*.[81]	No significant association was found between increased oral cancers and missing 16 or more teeth. The number of missing teeth and poor general oral condition at oral inspection had an increase in oral cancers
Garrote *et al*.[82]	The number of missing teeth and poor general oral condition at oral Inspection had an increase in oral cancers
Rosenquist *et al*.[83]	It was found that average oral hygiene, poor oral hygiene, more than five defective teeth, more than 20 missing teeth, and defective complete dentures were significant risk factors for development of oral and esophageal squamous cell carcinoma
Total cancer risk and periodontitis	
Cabrera *et al*.[84]	Did not find a relation between tooth loss and cancers in their study cohort
Michaud *et al*.[85]	After adjustment for known risk factors, such as smoking and diet, those with a history of periodontal disease had an increased risk of total cancer compared to those without a history. There were significant associations between Periodontal disease and lung, kidney, pancreatic and hematologic cancers. An inverse association was found for tooth loss and melanoma of the skin and advanced prostate cancer
Grant *et al*.[86]	Vitamin D status may be the underlying factor in the link between. Periodontal disease and tooth loss with cancer

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