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# Potential Co-Relation Between Chronic Periodontitis And Cancer – An Emerging Concept

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## Abstract

Periodontal disease caused chiefly by bacteria is characterized by inflammation, bacteremia, and a strong immune response. It is based on evidence that a continuous long-term exposure to oral bacteremia and bacterial toxins induces inflammatory immune response after immune evasion releases growth factors such as FGF, EGF, TGF-Beta, free radicals such as ROS and NOS, cytokines such as TNF-Alfa, IL-1 Beta, IL-6; and matrix metalloproteinase such as MMP-9. Immature myeloid cells such as macrophages, dendritic cells and granulocytes involved in chronic inflammation and tumor progression through immunosuppressive activity against innate and adaptive immunity by factors

such as iNOS, Arginase1 and ROS, activate major transcriptional factors such as NF-KB and STAT3 that could contribute to genetic instability, uncontrolled cell proliferation, angiogenesis, resistance to apoptosis, epithelial to mesenchymal transition, immunosuppression, invasion and metastasis. This study is a product of research and analysis on the role of chronic inflammatory mediators of chronic periodontitis in progression to cancer.

## Keywords

Myeloid-derived suppressor cells, LPS-lipopolysaccharide, TLR- Toll like receptor, MMP-Matrix metalloproteinase.

الأكسجين التفاعلية (ROS) وأنظمة أكسيد النيتروز (NOS)، والسيتوكينات مثل عامل نخر الورم ألفا (TNF-alpha)، وانترلوكين-1 بيتا (IL1) (beta) انترلوكين-6 (IL6). والبروتيناز الفزي المطرسي (MMP-9) والخلايا الناقية غير الناضجة كالبلاعم، الخلايا المتغصنة، والخلايا الحبيبية، تلك الخلايا المساهمة في الالتهابات المزمنة وتطور السرطان من خلال نشاط التثبيط المناعي ضد للمناعة الطبيعية والمكتسبة بواسطة عوامل عدة مخلقة أكسيد النترريك القابل للتحرير (iNOS) والأرجيناز 1 وأنواع الأكسجين التفاعلية (ROS)، كل أولئك ينشطون عوامل النسخ الرئيسية (NF-KB STAT3) والتي يمكنها المساهمة في عدم الاستقرار الجيني، والتكاثر غير المضبط للخلية، تولد الأوعية، مقاومة الموت المبرمج للخلايا (الاستماتة)، تحول

مفهوم جديد: العلاقة المحتملة بين التهاب دواعم السن المزمن والسرطان إن مرض دواعم السن سببه الرئيسي الجراثيم، حيث يتميز بالتهاب، تجرثم الدم، وقوة الاستجابة المناعية، العلاقة المفترضة في هذه الدراسة مبنية على البراهين التي أوضحت أن التعرض المستمر طويل المدى لتجرثم الدم الفموي والسموم الجرثومية يحفز الاستجابات المناعية الالتهابية بعد التهرب المناعي يفرز عوامل نمو كعامل النمو المحول - بيتا (TGF beta)، عوامل نمو الأرومة الليفية FGF وعامل النمو البشري (EGF)، كذلك الجذور الحرة كأصناف

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NF-KB = Nuclear factor kappa-light-chain-  
(enhancer of activated B cells

العامل النووي للخلايا البائية المنشطة بالمعزاز -  
خفيف السلسلة كبا .  
المصطلحات الأساسية : الخلايا الكاتبة المستتقة  
من النسيج النقوي ، عديد السكاريد الشحمي ،  
المستقبل شين Toll البروتيناز الفلزي .

النسيج الظهاري للمتوسطي ، الغزو والنقائل  
للأورام ، الاجتياح والانبثاق للأورام .

هذه الدراسة هي نتاج البحث والتحليل لدور  
الوسائط الالتهابية المزمنة لالتهاب دواعم السن  
في تطور السرطان .

STAT 3= signal transducer and activator 3 / 3  
ترجم الإشعار والمنشط للنسخ

## Introduction

Periodontal disease is an infection of the supporting structures of the teeth caused by bacteria. The host response to infection is an important factor in determining the extent and severity of periodontal disease. About 15–20% of cancers are linked to infectious diseases. Systemic factors modify periodontal diseases through their effects on the normal immune and inflammatory mechanisms. Severe oral infections, especially periodontal disease in otherwise healthy individuals, increase the risks in developing certain health problems including stroke, myocardial infarction and cancer.

## Background

The threat of periodontitis to overall health extends across the lifetime of an individual and it is associated with diabetes, smoking and poor oral hygiene. Bacteria causes periodontitis, yet the biochemical destruction that leads to clinical signs of disease is the result of the chronic inflammatory process in the periodontal tissues. Key bacteria are elevated in the subgingival plaque of patients with chronic periodontitis and have been identified as causing periodontal diseases like: porphyromonas gingivalis, Treponema denticola, bacteroids forsythus and A. actinomycetemcomitans. They require a lush biofilm ecosystem to support adherence, growth, emergence and reliance to host serum proteins and blood components for sustenance. These bacteria have special enzymes and proteins that enable them to trigger mild host inflammation<sup>(1,2)</sup>. Porphyromonas gingivalis is capable of evading neutrophil phagocytosis, invading through the epithelium to the tissues in to the bloodstream, secreting enzymes

that digest host tissues to enable penetration and spreading and triggering vasopermeability to facilitate hematogenous dissemination.

The bacteria have been identified at many distant sites, such as within athermanous plaques, fetal cord blood, pneumonia areas, brain abscess, eye and skin inflammatory reactions. Oral bacteria have been linked to infections of the endocardium, meninges, mediastinum, vertebrae, Hepatobiliary system and prosthetic joints<sup>(3-4)</sup>. P. gingivalis avoids activating the acquired immune response and evades immune surveillance and clearance by concurrent activation of autophagy and suppression of apoptosis; invasion of vascular endothelial cells is dependent on fimbriae and a specific hemagglutinin<sup>(5-7)</sup>. Fimbriae in P. gingivalis induce IL-6 in vascular endothelial cells and other infectious, inflammatory mediators like TNF- Alpha, IL-1 beta, LPS, PGE2, HSP72; activates transcriptional factors nuclear factor kappa (NF-kB) and activator - protein (AP- 1), STAT-3 which regulates apoptosis, cell proliferation and angiogenesis. These promote cell survival by upregulating expression of anti-apoptotic genes and of genes regulating cell cycle checkpoints, including C-MYC, MC-1, Cyclin-D, Bcl-2, C-Flip and survivin, thus further alters cellular genomic instability<sup>(8-11)</sup>.

## Discussion

Other periodontal pathogens also appear to gain systemic egress and become blood borne. It has been suggested that the periodontal pocket epithelium surface area can approximate a wound site for microbial penetration<sup>(6)</sup>. In patients with periodontal pathogen, bacteremia occur and initiate a systemic antibody response and activation of the hepatic

acute– phase response. The liver can be activated by bacteria, bacterial products such as LPS, cytokines like IL–1 beta, TNF – Alpha, matrix metalloproteinase–2, vascular cell adhesion molecule–1, and IL–6. This activation results in the synthesis of acute phase proteins such as CRP. Inflammation and bacteria at a systemic low grade level when repeated acutely and aggravated chronically provide severe cumulative damage to systemic health <sup>(9,12,13)</sup>. Periodontal pathogens also create toxic lipopolysaccharide (LPS) that is highly inflammatory. The LPS is released within the pockets and penetrates into the tissues where the LPS interacts with macrophages to stimulate the release of inflammatory mediators such as PGE2, IL–1 beta, TNF– Alpha, IL–8, MMP–9. These inflammatory markers cause vasodilation and destruction of the periodontal ligament, activate fibroblast and osteoclasts to tissue destruction and bone resorption <sup>(11)</sup>. Periodontitis has a genetic component; certain genes associated with an excess production of IL–1beta have been associated with severe periodontal disease and much of the susceptibility to disease is inherited. Smoking and diabetes, not plaque accumulation, enhance the inflammatory response to bacterial LPS, while also impairing the ability to fight infection by compromising neutrophil function <sup>(14,15)</sup>. TNF– Alpha is a proinflammatory and immunoregulatory cytokine central to the pathogenesis of various inflammatory conditions <sup>(16,17)</sup>. It plays a role in the recruitment of inflammatory cells and bone resorption through its ability to stimulate IL–1 and granulocyte macrophage colony–stimulating factor (GM–CSF) <sup>(18–21)</sup>. This exaggerated inflammatory response results in more severe periodontitis in patients with diabetes and smokers results in production of myeloid derived suppressor cells (MDSC).

MDSC are heterogeneous immature myeloid cells that fail to terminally differentiated into granulocytes, macrophages or dendritic cells upon chronic inflammatory conditions and exhibit immunosuppressive functions by multiple mechanisms <sup>(32)</sup>. These cells are heterogeneous and therefore their phenotypical characteristics are broadly distinct. Among human MDSCs, the two subsets are monocytic and granulocytic <sup>(22)</sup>. Myeloid derived suppressor cells derive from the bone marrow hematopoietic precursors by chronic

inflammatory mediators such as IL–1 Beta, IL–6, PGE2, CCL2, CXCL5, TNF–Alfa and S100A8/A9, which alters myelopoiesis. MDSC survival and proliferation are regulated by transcriptional factor STAT3. These are the major immunosuppressor cells that cross–talk with other immune cells such as CD8 T cells and NK cells to inhibit both adaptive and innate immunity by iNOS, Arginase1, ROS and Cysteine deprivation mediated T cell suppression. iNOS to break down L–arginine in to nitric oxide which inhibits T– cell activation and abrogates expression of MHC11 molecule on antigen presenting cells. Arginase1 breaks down L–arginine into urea and L–ornithine. L–arginine depletion prevents T–cell function. ROS induce apoptosis of T–cell and prevents cytokine secretion by T–cells. Cysteine deprivation mediated T–cell suppression, an amino acid essential for T cell activation <sup>(23–27)</sup>. MDSC promotes tumor–associated angiogenesis by matrix metalloproteinases (MMP–9), VEGF and bFGF facilitate cell invasion and intravasation by secreting proteolytic enzymes such as MMP, induce epithelial mesenchymal transition in cancer cells using EGF (Epithelial growth factor), HGF (Hepatocyte growth factor) and TGF–Beta <sup>(28–32)</sup>.

Reactive Oxygen Species (ROS) is an abundant, unstable, highly reactive, mutagenic factor frequently present in inflammatory microenvironment as a result of oxidative stress and induced by phagocytic cells. It causes DNA damage and changes cell mutation rate, thus enhancing the appearance of clones with oncogenic properties <sup>(33,34)</sup>. Inflammatory factors promoting proliferation are TGF–beta, Fibroblast growth factor (FGF), and epithelial growth factor. TGF–beta is a cytokine orchestrate and regulate growth and differentiation in all cell types and tissue. It synthesizes as an inactive precursor due to mutation or deletion by macrophages, mast cells and lymphocytes activated by proteases in inflammatory microenvironment, promotes epithelial mesenchymal transition (EMT) by enhancing the degradation of extracellular matrix leads to invasion, angiogenesis and metastasis <sup>(35, 36)</sup>. Activated macrophages are antigen presenting cells produce proliferating factors like EGF, FGF, IL–6 and IL–8 which are a mitogenic trigger of fibroblast, epithelial and endothelial cells promotes cell proliferation and angiogenesis <sup>(37–41)</sup>.

LPS is a known activator of macrophage which, cross talk with MDSC in the presence of LPS.

Later, LPS binds to LPS binding protein which helps in transfer of LPS to the membrane bound receptor CD14 through TLR4 signaling pathway. TLR4 signaling pathway gets activated when CD14 binds with TLR4. Further, downstream activation of NF- $\kappa$ B driving MDSC production of IL-10 resulting in immunosuppression and immune evasion by promoting M2 polarization of macrophages. M2 macrophages are alternatively activated and promotes tumor progression by secreting IL-10, VEGF and PGE2 on exposure to hypoxia. All these factors favor towards pro-inflammatory to pro-tumoral activity which results in onco-promotion, onco-training, and tumor formation. Periodontal micro-organisms are found in different sites. There is a potential link between chronic periodontitis in pathogenesis of cancer. Chronic inflammation is considered to be a seventh hall mark of cancer<sup>(33, 42)</sup>.

## Conclusion

Periodontal bacteria are known to evade immune cells, invade the systemic circulation, release inflammatory mediators such as cytokines (IL-6, IL-8, TNF- $\alpha$ ) and growth factors (EGF, FGF), PGE2, free radicals (ROS, RNS), and matrix metalloproteinases from inflammatory cells such as macrophages, lymphocytes and myeloid derived suppressor cells. Intermittently, this reaches the blood stream, inducing chronic, low-level bacteremia and systemic inflammatory-immune reactants to activate transcriptional factors such as NF- $\kappa$ B and STAT3 – all of which could represent a pathogenetic link between periodontal disease and cancer by genetic mutation, cellular proliferation, resistance to apoptosis, epithelial to mesenchyme transition, angiogenesis, invasion and metastasis. Cancer is a condition of global health concern because of increased mortality and morbidity. Interaction between periodontal microbes, immune cells and its association with cancer remains to be established. It is in the interest of public health to address this issue to improve patient care and the development of therapeutic applications for this condition.

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