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# Looking in the *Porphyromonas gingivalis'* Cabinet of Curiosities: The Microbium, the Host and Cancer Association

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## Summary

The past decades of biomedical research have yielded massive evidence for the contribution of microbiome in the development of a variety of chronic human diseases. There is emerging evidence that *Porphyromonas gingivalis*, a well-adapted opportunistic pathogen of the oral mucosa and prominent constituent of oral biofilms, best known for its involvement in periodontitis, may be an important mediator in the development of a number of multifactorial and seemingly unrelated chronic diseases, such as rheumatoid arthritis and orodigestive cancers. Orodigestive cancers represent a big portion of the total malignancies worldwide, and include cancers of the oral cavity, gastro-intestinal tract, and pancreas. For prevention and/or enhanced prognosis of these diseases, a good understanding of the pathophysiological mechanisms and the interaction between *P. gingivalis* and host is much needed. With this review, we introduce the currently accumulated knowledge on *P. gingivalis'* plausible association with cancer as a risk modifier, and present the putative cancer promoting cellular and molecular mechanisms that this organism may influence in the oral mucosa.

> "Knowledge is made by oblivion, and to purchase a clear and warrantable body of truth, we must forget and part with much we know"
>
> Sir Thomas Browne (1605–1682)

## Introduction

The last few decades of biomedical research have accumulated a large knowledge base on the etiopathogenic mechanisms of numerous chronic diseases and conditions of man. In many of these chronic pathologies, bacteria have been shown to play a major role either as singular etiologic factors, or as synergistic contributors in the multifaceted stimulation of the host immune system that can tip the scales towards chronic or autoimmune disease development. Recent advances in metagenomic tools have heightened the importance of resident microbiome in mammalian development, metabolism, immune response and behavior during all stages of life, which has led to the initiation of several world-wide projects to determine the species diversity and genetic make-up of the human microbiome in health and disease (Diaz Heijtz *et al.*, 2011, Cox *et al.*, 2013, Erturk-Hasdemir & Kasper, 2013, Guinane & Cotter, 2013, Mavrommatis *et al.*, 2013, Ridaura *et al.*, 2013). Multiple specific examples may be given for the growing role of the human microbiome in development of chronic pathological conditions. These include chronic inflammatory diseases of the lung, liver, cardiovascular and digestive systems, as well as of periodontium (Berry & Reinisch, 2013, Chassaing *et al.*, 2013). The human microbiome contains a

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number of adaptable pathogenic species that are now identified to be closely involved in the etiology of various chronic diseases. One of the best documented examples is a Gram-negative bacterium, *Helicobacter pylori*, primarily known for its involvement in gastric and gastro-intestinal cancers, and more recently in other chronic diseases, including asthma, type2 diabetes, and obesity (Wang *et al.*, 2013). Furthermore, increasing evidence suggests that the establishment of a variety of chronic diseases could result from a polymicrobial interactions within the underlying microbiome, in concert with host genetic and metabolic risk factors (Michaud, 2013, Wroblewski *et al.*, 2010, Fox & Sheh, 2013).

The human body represents a multitude of mucosal sites, each comprising a specific milieu of highly adapted, commensal and opportunistic-pathogen organisms. One of the most complex and highly variable communities is the oral microbiome, which has long been implicated in the development of tooth decay and periodontal disease (Jenkinson, 2011). The oral microbiome represents a unique and vastly dynamic multidimensional biochemical network, formed by the interaction among the proteomes and metabolomes of the comprising organisms, the behavioral, hygienic and dietary habits of the host, and the genetic and immunologic host factors (Jenkinson, 2011, Khalili, 2008, Teles *et al.*, 2013, Wright *et al.*, 2013). Some of these interactions yield potentially pathogenic compounds that may have effect on the mucosal lining, the surrounding tissues and even on the distant organs and systems of the body (Hooper *et al.*, 2009, Jenkinson, 2011, Ahn *et al.*, 2012a). Those noxious metabolic products or molecules include lipids, lipopolysaccharides (LPS), free oxygen and nitrogen radicals, pro-inflammatory mediators and host and/or bacteria derived enzymes. Hence, the oral microbiome has been proposed to impact the etiology and progression of diabetes, cardiovascular disease, and lately a number of studies have indicated the association among distinct consortia of microbial species, periodontal disease and orodigestive cancers (Koren *et al.*, 2011, Ahn et al., 2012a, Meyer *et al.*, 2008). The evidence accumulated from those studies has specified strong correlation among a number of chronic periodontal bacteria containing *Prevotella*, *Porphyromonas Fusobacterium*, and *Streptococcus spp.*, and squamous cell carcinoma of the orodigestive tract, which encompasses the oral cavity, gastro-intestinal tract and pancreas (Nagy *et* al. 1998, Mager *et al.*, 2005,, Ahn *et al.*, 2012b).

Among these specific species, an opportunistic pathogen, *Porphyromonas gingivalis*, has emerged as a potential mediator in the etiology of a variety of presumably unrelated chronic diseases, such as rheumatoid arthritis, cardiovascular diseases, diabetes, and more recently different types of orodigestive cancers (Ahn et al., 2012b, Hitchon *et al.*, 2010, Totaro *et al.*, 2013, Ishikawa *et al.*, 2013, Aemaimanan *et al.*, 2013, Katz *et al.*, 2011,, Michaud, 2013, Hajishengallis *et al.*, 2012). In the case of rheumatoid arthritis, *P. gingivalis'* peptidylarginine deiminase (PAD) has been recently suggested to assume a key role in the citrullination of arginine residues in host proteins, thus altering their normal folding and creating conditions for the induction of auto-antibodies against host cartilage-specific antigens. *P. gingivalis'* ability to activate host matrix metalloproteases (MMPs) and the organisms' role in altering cytokine responses have also been implicated in the protein degradation, observed in arthritic joints (Mangat *et al.*, 2010, Hitchon et al., 2010, Detert *et al.*, 2010). Conjointly, prolonged systemic cytokine elevation and inflammation have been especially attributed to *P. gingivalis* in the context of the multifactorial periodontal disease as contributing and/or amplifying factor in the development and progression of diabetes mellitus. The poor glycemic control in diabetes, on the other hand, has been shown to exacerbate chronic periodontitis (Lalla & Papapanou, 2011). A significant statistical association has been also observed between *P. gingivalis*-carriage in saliva samples and non-alcoholic fatty liver disease, further strengthening *P. gingivalis*' role as a risk factor in multiple chronic conditions (Yoneda *et al.*, 2012).

On the cancer front, multiple clinical and experimental studies have displayed various degrees of associations between *P. gingivalis* and cancers of the oral cavity, orodigestive tract or pancreatic tissues (Katz et al., 2011, Groeger *et al.*, 2011, Michaud, 2013, Michaud *et al.*, 2012, Ahn et al., 2012b).

*P. gingivalis*, which has been shown to have the plenitude of virulence factors, can also be present in healthy individuals' periodontal pockets, affluently survives within oral epithelial tissues, and is successfully able to evade the host immune response (Yilmaz, 2008, Choi *et al.*, 2013, Yilmaz *et al.*, 2008, Singh *et al.*, 2011, Yao *et al.*, 2010, Yilmaz *et al.*, 2010). Accordingly, *P. gingivalis* has recently been attributed as a key-stone pathogen based on its ability to orchestrate inflammatory disease by remodeling the oral microbiome (Hajishengallis et al., 2012). *P. gingivalis*, can invade primary cultures of oral epithelial cells (OECs), render them resistant to cell death, and alter the chemokine and cytokine secretion (Spooner & Yilmaz, 2011, Choi et al., 2013, Yilmaz et al., 2010, Yao et al., 2010, Hung *et al.*, 2013, Takeuchi *et al.*, 2013). OECs that form the outer lining of the oral mucosa are the initial targets for colonizing bacteria, and stand an important arm of the host innate immune response by secreting antimicrobial, pro-inflammatory and chemotactic signals, and modulating apoptosis upon sensing invading organisms (Takeuchi et al., 2013, Yilmaz et al., 2010, Hung et al., 2013). Therefore, the ability of *P. gingivalis* to colonize in the oral cavity and modulate both the epithelial cell and systemic responses potentially places the organism not only in the category of central contributors in the multifactorial etiology of the periodontal disease, but also orodigestive cancers and other chronic diseases (Figure 1).

The prospective multiple roles of *P. gingivalis* in the above mentioned conditions, however, remain incomplete and there is a clear need for mechanistic determination of these newly observed associations in order to better understand and possibly control those severe chronic conditions. Therefore, this review aims to offer a fresh perspective on the putative role of *P. gingivalis* in the orodigestive cancers, and its plausible use as a biomarker for the identification of at "high-risk" populations.

## P. gingivalis and Cancer

The significance of *P. gingivalis* involvement in cancer has evolved within the last decade. Chronologically initial studies have comprised mostly epidemiological and clinical association between oral microbiome, periodontal disease or tooth loss, with orodigestive cancers including cancers of the oral cavity, gastrointestinal tract and pancreas (Hooper *et al.*, 2009, Ahn et al., 2012a, Meyer et al., 2008, Katz et al., 2011, Groeger et al., 2011, Michaud, 2013, Ahn et al., 2012b). Among all observed cancer relations the most direct and strong association of *P. gingivalis* has been found with oral squamous cell carcinoma (OSCC) (Nagy *et al.*, 1998, Mager et al., 2005, Katz et al., 2011). OSCC is one of the highly common cancers in the United States with estimated 35,000 newly diagnosed cases and over 7,500 deaths occurring yearly (Jemal *et al.*, 2008). Currently there is a lack of reliable diagnostic tools for identification of high-risk persons, most OSCC cases have metastases already at presentation, and available therapies fail to prevent malignant progression (Mitka, 2013). All these factors support the necessity for early markers that can identify the risk populations and possibly be used for preventative care, before carcinogenesis develops.

### 1. Historical Perspective and Clinical Relevance

Among the first studies to examine association between periodontitis and cancer was a case-control study conducted between 1999 and 2005 in the USA that examined 473 patients (Tezal et al., 2009). The study measured periodontitis by alveolar bone loss and screened the patients for squamous cell carcinoma of the oral cavity, pharynx and larynx. Chronic periodontitis was associated with 4-fold increase in risk of any of the three examined types

of carcinoma. The strength of the association was greatest with cancers of the oral cavity, followed by the oropharynx and larynx. The association persisted in subjects who never used tobacco and alcohol, which suggests chronic periodontitis to be an independent risk factor for the cancer development (Tezal et al., 2009).

One of the initial broad surveillance studies showing potential link between *P. gingivalis* and orodigestive cancers was the National Health and Nutrition Examination Survey III (Ahn et al., 2012b). This prospective study included a total of 12,605 men and women with clinically ascertained periodontitis of which 7,852 had serum IgG immune response to *P. gingivalis.* They were followed from 1988 through 2006 in relation to orodigestive cancer mortality, including cancers of the lip, oral cavity, gastrointestinal tract, pancreas and liver, and in that period 105 orodigestive cancer deaths occurred. Moderate or severe periodontitis was found to be associated with increased orodigestive cancer mortality relative risk. The mortality risk was also proportionally increased with increasing severity of periodontal disease. The highest association with periodontitis was found for colorectal and pancreatic cancer, whereas greater serum *P. gingivalis* IgG levels tended to be associated with increased orodigestive cancer mortality (Ahn et al., 2012b). Interestingly, *P. gingivalis* was also associated with 2.25-fold higher likelihood for orodigestive mortality in healthy subjects not exhibiting overt periodontal disease. Hence, this study was the first to illustrate direct correlation of orodigestive cancer mortality to *P. gingivalis* independently of periodontal disease, thus pinpointing that *P. gingivalis* could be a valuable biomarker for microbe-associated risk of orodigestive-cancer-death (Ahn et al., 2012b).

In 1998, a study compared biofilm samples from central ulcerating surfaces of OSCC lesions and healthy mucosa from 21 middle aged, prevalently male patients without antibiotic or tumor therapy (Nagy et al., 1998). The study found a significantly higher number of both specific anaerobic and aerobic bacterial species at the tumor sites compared to healthy mucosa. Interestingly the genus *Porphyromonas* was identified among the genera with highest rates of isolation at the tumor sites (Nagy et al., 1998). More than a decade later, in 2012, a similar study quantitated the 16S ribosomal DNA fragments from six periodontal bacteria including *P. gingivalis* in formalin-fixed, paraffin-embedded lymph nodes from 66 patients with histories of head and neck cancers, including OSCC (Amodini Rajakaruna *et al.*, 2012). The lymph nodes selected for the study did not have metastatic invasion yet. The relationship between bacterial detection and cancer severity, gender, and the use of anti-cancer therapy was examined by Fisher's exact test and was not found to be statistically significant. However, *P. gingivalis* was detected in the samples of submandibular and submental lymph nodes of ~ 20% of these patients, and the study suggested that translocation of periodontopathic bacteria may occur via lymphatic drainage, irrespective of the cancer disease status or therapy (Amodini Rajakaruna et al., 2012).

In a 2005 study an increased ratio of *P. gingivalis* in saliva samples of 45 OSCC patients compared to 229 healthy subjects was reported. While this increase was not statistically significant, this was perhaps due to the relatively small patient size (Mager et al., 2005). On the other hand, a recent analysis of oral tissue samples from 10 cases and 5 healthy individuals using anti-*P. gingivalis* (ATCC33277)-specific immunohistochemistry detected a statistically significant increase of *P. gingivalis* staining in OSCC tissues than normal tissues. The study used antibody staining against the commensal bacterium *Streptococcus gordonii* as a control, which did not show any significant distribution difference (Katz et al., 2011). This finding highlighted for the first time a noteworthy association of *P. gingivalis* with OSCC, despite the low sample size.

Another study from 2012 that measured plasma antibodies to 25 oral bacteria in pre-diagnostic blood samples from 405 pancreatic cancer patients and 416 matched controls also

indirectly associated *P. gingivalis* with increased risk of pancreatic cancer. The study demonstrated high correlations for two strains of *P. gingivalis* (ATCC 53978 and 33277). Individuals with high levels of antibodies against *P. gingivalis* ATTC 53978 had a two-fold higher risk of pancreatic cancer than individuals with lower levels of anti-*P. gingivalis* antibodies (Michaud et al., 2012). A year later in a clinical study involving 37 cases of chronic atrophic gastritis, intestinal metaplasia, or dysplasia, DNA levels of periodontopathic bacteria, including *P. gingivalis*, were measured in plaque and saliva samples by real-time quantitative PCR (Salazar *et al.*, 2013). An elevated but not statistically-significant odds ratio for gastric precancerous lesions was observed in relation to increasing colonization with *P. gingivalis*, *Aggregatibacter actinomycetemcomitans* and *Treponema denticola* measured in plaque, and thus the study associated high levels of periodontal-pathogen colonization with an increased risk of gastric precancerous lesions in individuals with periodontal disease (Salazar et al., 2013). A recent case-control study examined the fecal microbiome changes of 19 colorectal cancer patients in comparison to 20 healthy people using 16S rRNA pyro-sequencing (Wu *et al.*, 2013). Interestingly, although the study was not designed to screen for specific bacterial species, it detected a highly statistically significant increase of *Porphyromonadaceae* family, along with *Fusobacteriaceae*, and 3 other operational taxonomic units in the colorectal cancer patients compared to the healthy subjects (Wu et al., 2013).

All these studies underlined the plausible role of *P. gingivalis* in the variety of orodigestive cancers described, and prompt many questions on the possible mechanistic bases of the detected associations. Answers to such questions may be obtained through the use of physiologically relevant *in vitro* studies. The rest of the review is dedicated to describe the presently available work that exist in the literature and will provide further insights.

## 2. In Vitro Studies and Potential Mechanisms

Although there is mounting clinical evidence links *P. gingivalis* and/or periodontal disease with orodigestive cancer risk, there are currently only several *in vitro* reports that directly studied the carcinogenic potential of *P. gingivalis*. Based on the new information flowing and the available new technologies, there is a new charge for the scientific community to investigate the emerging role of *P. gingivalis* in the increased risk of cancer development.

**2a. Findings in Vitro with Oral Cancer Cell Lines—**In 2011, a study utilized two OSCC-derived cell lines, the metastogenic ‘SCC-25’ and non-metastatic ‘BHY’ cells, as well as human primary oral epithelial cells (OECs), to examine the expression of two human B7-homologue receptors, ‘B7-H1’ and ‘B7-DC’ (Groeger et al., 2011). These receptors have been found to be highly expressed in the majority of human cancers. Receptor B7-H1, mostly known as programmed death ligand 1, is an important regulator in cell-mediated immunity by promoting the development of regulatory T cells, and is thought to play a major role in suppressing the immune system during cancer (Greaves & Gribben, 2013). B7-DC, also known as programmed death ligand 2, is expressed mainly on dendritic cells and macrophages, although it can be induczed in a variety of cell types and is suggested to suppress T-cell survival, cytokine production and proliferation (Rozali *et al.*, 2012). In the study, Groeger and colleagues demonstrated a significant upregulation of both B7-H1 and B7-DC receptors in the metastogenic SCC-25 cell line and in human primary OECs after infection with *P. gingivalis* strains ATCC 33277 or W83. In contrast, infection with *Streptococcus salivarius* K12, a commensal bacterium used as a control in the study, did not have any effect on the examined receptors that are important for cancer etiology (Groeger et al., 2011). These findings strongly suggest a potential role for *P. gingivalis* in contributing to the cellular / molecular changes promoting oral cancer, possibly through facilitating immune evasion.

An earlier *in vitro* study examined the effect of *P. gingivalis'* LPS on cancer progression of an OSCC derived cell line, 'YD-10B', which has been shown to express functional Toll-like receptors (Park *et al.*, 2010). The study showed no effect of *P. gingivalis* LPS on the cell proliferation, migration, invasion or angiogenesis, which are the mechanisms shown to be involved in various cancer development (Park et al., 2010). The study, however, used purified LPS, and was not designed to study the outcome of complete *P. gingivalis* infection on the cancer cell line, thus excluding the possible roles of other virulence factors of the bacterium in this model. This result may suggest that the reputed role of *P. gingivalis* is possibly not due to one singular component, but is likely a greatly concerted synergistic play, requiring other structural properties, and potentially dynamic bacterium-host interaction.

Very recently, another study examined the effect of *P. gingivalis*, using strain ATCC 33277, on the metastatic ability of two OSCC cell lines, the highly metastogenic 'SAS' cells and the low-metastogenic 'Ca9-22' cells (Inaba *et al.*, 2013). Metastatic invasion was measured by the induction and activation of human matrix metalloproteinase 9 (MMP9) in the cells upon infection with *P. gingivalis* compared to another periodontal organism *Fusobacterium nucleatum.* In SAS cells wild-type *P. gingivalis* ATCC 33277 was able to increase basal expression of proMMP9 enzyme and subsequently to activate MMP9, whereas *F. nucleatum* did not alter expression or activation of proMMP9. In the less-metastatic Ca9-22 cell line, *P. gingivalis* infection did not have directly observed effect on pro-MMP9 expression or activation, although incubation of Ca9-22 cells with supernatant of *P. gingivalis*-infected SAS cells increased Ca9-22 cells' metastogenic capacity significantly. Using gingipain mutant strains, the production and activation of proMMP9 was shown to be dependent on gingipains of *P. gingivalis*. The study also showed that proMMP9 production was controlled by the phosphorylation of the heat-shock-protein 27, HSP27, which was previously found to be over expressed in OSCC tissues (Turhani *et al.*, 2006). *P. gingivalis* may hold the potential to contribute to the cancer progression and mediate enhanced host-cell metastatic potential by activation of MMP9 via its gingipain proteases (Inaba et al., 2013).

Collectively, these studies substantiate the growing plausible role of *P. gingivalis* in cancer etiology, rather than being a bystander, although there has been a view that the opportunistic bacteria may come after the disease-induced suppression in immunity and compromised mucosal integrity (Cummins & Tangney, 2013). Therefore, it is important to recognize that studying pre-cancerous lesions of the oral mucosa, before malignancy, is perhaps the most relevant stage to examine the direct involvement of pathogens in cancer formation. The following section of this review will illustrate at present knowledge derived from human primary OECs and oncogenesis-related pathways, and highlight plausible mechanisms for *P. gingivalis'* connection in the cellular / molecular mechanisms that are cancer promoting.

**2b. Relevant Findings with Human Primary Oral Epithelial Cells—***P. gingivalis*-host interaction studied in the primary cultures of the OECs has proven to be an invaluable model to appreciate the highly orchestrated, complex nature of the interface between the chronic organism and the oral epithelium, as the OECs can emulate the *in vivo* characteristics of human mucosal epithelium most closely. During those studies, the human primary OEC model provided substantial mechanistic insights on the *P. gingivalis'* persistence strategies in the oral epithelium that may well be pertinent in the orodigestive cancer etiology and/or advancement.

*P. gingivalis* was shown to rapidly invade the primary OECs in culture by using the β1-integrin and downstream signaling pathways, and can spread intercellularly later in the infection using actin cytoskeleton, thus evading recognition by the immune system (Yilmaz, 2008). Using *P. gingivalis* strain ATCC 33277 the organism was demonstrated to inhibit

OEC programmed cell death induced by potent pro-apoptotic agents. The characterized epithelial-host-survival molecular actions of *P. gingivalis* include blocking of mitochondrion-dependent apoptosis (by inhibition of cytochrome-c release, mitochondrial membrane depolarization, balancing of pro-apoptotic Bax and anti-apoptotic Bcl-2 expression), activation of the phosphatidylinositol 3 kinase (PI3K) / Akt and survivin / Stat-3 survival pathways, inhibition of caspase-3 and 9 activation, and inactivation of pro-apoptotic Bad-signaling (Nakhjiri *et al.*, 2001, Mao *et al.*, 2007, Yilmaz, 2008, Yao *et al.*, 2010). PI3K / Akt and Survivin / Stat-3 are well described as key regulators of cellular processes that can lead to initiation and/or maintenance of carcinogenesis. Both of the pathways are currently evaluated as major therapeutic targets in cancer (Altieri, 2003). The studies with the human primary OECs also revealed that *P. gingivalis* infection promotes pro-survival phenotype in the host cells by accelerating the progression through the S-phase of the cell cycle via the modulation of pathways involving cyclins and p53 (Yilmaz, 2008, Kuboniwa, M *et al*., 2008). The infection by the organism is able to alter the expression of 'p53 tumor suppressor', which is known to be involved in DNA-damage-response and in tumor suppression (Ozaki *et al.*, 2013). The aforementioned actions of *P. gingivalis* appeared to be dependent on presence of the major fimbriae (FimA) of the organism (Kuboniwa *et al.*, 2008). Furthermore, *P. gingivalis* can inhibit OEC cell death induced by an important physiological pro-apoptotic molecule, extracellular ATP. ATP elicits its activity through the purinergic cell surface receptor, $P2X_{7,.}$ The ATP coupled $P2X_7$ signaling has direct implications for regulating of a variety of specific host immune response elements that are lately shown to be critically involved in pathways towards carcinogenesis (Adinolfi *et al.*, 2012, Chadet *et al.*, 2014, Di Virgilio, 2012, Jelassi *et al.*, 2013, Roger & Pelegrin, 2011). Some of these actions include the modulation of intracellular reactive oxygen species (ROS), controlling of apoptosis, activation of inflammasome, and secretion of pro-inflammatory cytokines. The recent efforts in the treatment and invasiveness of several types of cancers with high mortalities are directly targeted against $P2X_7$ / ATP-signaling, and $P2X_7$ expression has been found in diverse tumors and has newly been proposed as a potential cancer cell biomarker (Huang *et al.*, 2013, Roger & Pelegrin, 2011). *P. gingivalis*' inhibition of ATP / $P2X_7$-induced cell-death in OECs is mediated by secretion of an ATP-utilizing enzyme, nucleoside diphosphate kinase (NDK) (Spooner & Yilmaz, 2012, Choi *et al.*, 2013). NDKs have recently emerged as a novel secreted effector for successful persistence by chronic opportunistic pathogens, such as *Mycobacterium tuberculosis* and *Pseudomonas aeruginosa* (Yilmaz, 2008). A new study further demonstrated that *P. gingivalis* can modulate ATP-induced cytosolic and mitochondrial ROS as well as antioxidant glutathione response generated through $P2X_7$ / NADPH-oxidase interactome via temporal secretion of the NDK (Choi *et al.*, 2013). ROS can serve as a key mediator in activation of a selection of cancer / inflammation associated transcription factors (Spooner & Yilmaz, 2011).

Intriguingly, NDK species, including the human homologues known as 'non-metastatic cells expressed proteins' (NME), encoded by nm23 genes, are recently widely studied for their involvement in various forms of human cancers, such as breast, lung, thyroid and neuroblastoma cancers, as well as for metastasis and regulation of p53-mediated transcription (Prabhu *et al.*, 2012, Marino *et al.*, 2012, Boissan & Lacombe, 2011). Most interestingly, the human NDK was shown to be over expressed in surgically excised tumor-tissues of OSCC patients, compared to healthy mucosa from the same patients (Turhani et al., 2006). The study identified only 20 proteins with altered expression in OSCC tissue and intriguingly human NME1 and HSP27 were among the 14 proteins with significantly increased levels.

Notably, ATP / $P2X_7$-signaling is lately associated with the development of multiple pathologic conditions in addition to cancer such as diabetes, obesity, multiple sclerosis, joint

disease, pancreatic disease, and kidney diseases. The significance of $P2X_7$ receptor's splice and polymorphism variants in chronic human diseases is also becoming an active area of research (Hillman *et al.*, 2005, Adinolfi *et al.*, 2012, Di Virgilio, 2012, Chen *et al.*, 2011, Garcia-Hernandez *et al.*, 2011, Sun *et al.*, 2012, Oyanguren-Desez *et al.*, 2011, Lopez-Castejon *et al.*, 2010). $P2X_7$ is known to play a critical role in promoting cell growth, neovascularization, tumor-host interactions, and metastasis, and can induce release of cathepsins by macrophages (involved in joint diseases) markedly increased in chronic and inflammatory conditions (kidney disease, diabetes). It is worth emphasizing that this assembly of diseases is similar to the array of chronic conditions recently being associated with presence of *P. gingivalis* (Aemaimanan et al., 2013, Ahn et al., 2012b, Hitchon et al., 2010, Katz et al., 2011, Michaud, 2013). Moreover, molecular actions of *P. gingivalis* have been shown to be highly cell-type dependent and different outcomes may be stimulated in different cell types. These interactions are further complicated by the fact that *P. gingivalis*' colonization in the oral mucosa is closely accompanied by multiple bacterial species. Intriguingly, among those oral organisms, *F. nucleatum* is newly associated with progression of malignant tumors of intestinal system particularly colorectal cancer (Kostic *et al.*, 2013, Rubinstein *et al.*, 2013), thus making the entire host-pathogen interaction much more complex.

Taken together, *P. gingivalis*' shown ability to modulate ATP / $P2X_7$-signaling, to secrete an anti-apoptotic enzyme, NDK during the infection of primary OECs, and to express other virulence factors (e.g. fimbriae, gingipains, PAD) may serve as potential etiologic links with orodigestive cancers and possibly other chronic diseases. The postulated stepwise transformation of the normal epithelium to the precancerous and cancerous lesions in the presence of *P. gingivalis* infection and the plausible associated pathways are sketched in Figure 2.

## Conclusion and Future Studies

The potential significance of *P. gingivalis* is rapidly rising in the OSCC etiology and the other cancers of the orodigestive tract. *P. gingivalis* is thought to have co-evolved with humans since the divergence of the Old World monkeys of Africa around 6–7 million years ago (Mikkelsen *et al.*, 2008). One can speculate this long co-existence may have brought the excellent adaptation of this successful persistent bacterium to the human oral mucosa. Cancer is considered to be a disease of civilization. It is possible that *P. gingivalis* has recently evolved to become a risk factor in the cancer etiology. Conceivably, the advancements in society, the global ecological changes, and increase in human longevity have allowed the increase of many of the current chronic diseases, and stimulated the rise of a range of currently unknown virulence factors of *P. gingivalis.* Nevertheless, the aforementioned possibilities remain to be further researched.

In summary, oral mucosa harbors vast numbers of naturally occurring microbes on the epithelial surfaces, which might have direct synergistic or antagonistic effects on the occurrence and or advancement of precancerous and cancerous formations in the oral cavity. The centrality of *P. gingivalis* to orodigestive cancer is still debated, however, in light of the recent findings, we propose the organism is perhaps an important predisposing factor in the microenvironment that directs the development or poor prognosis of orodigestive cancers and possibly other chronic diseases. Future large-scale integrated clinical and *in vitro* mechanistic studies accompanied by *in vivo* validation assays may determine the specific microbial components and the associated microbiome populations that may well participate in cancer and the complex bacteria-host interaction contributing to these devastating chronic diseases.

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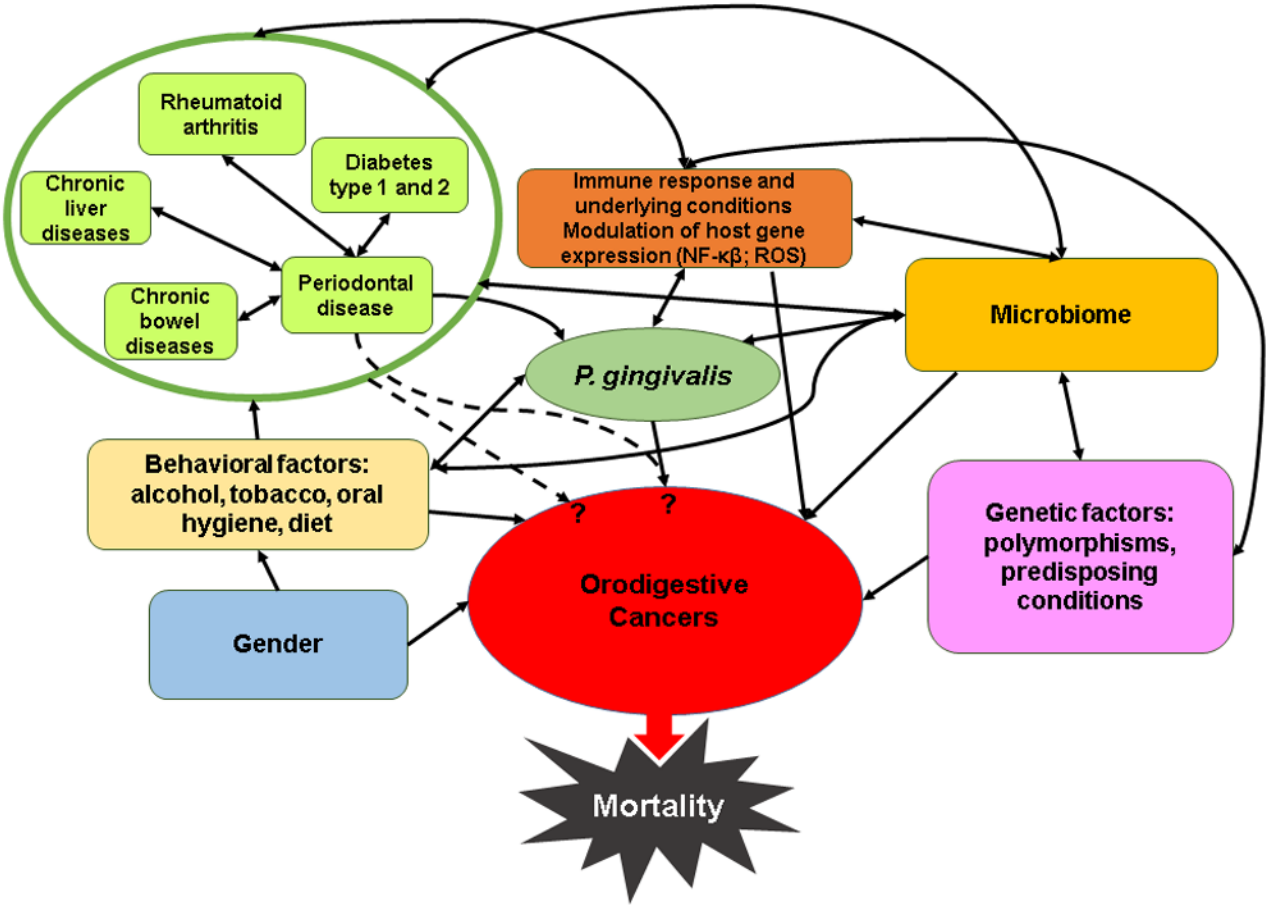


**Figure 1.**

Schematic representation of the complex interrelationships between different human genetic, behavioral and immunologic factors, as well as microbiome-related factors, that are proposed to take part in the multifactorial etiology of orodigestive cancers and other possibly associated chronic diseases. *P. gingivalis* is implicated to play a specific role in these multi-directional links. Dashed arrows represent plausible associations, based on currently available epidemiologic, clinical, histological, and experimental studies.

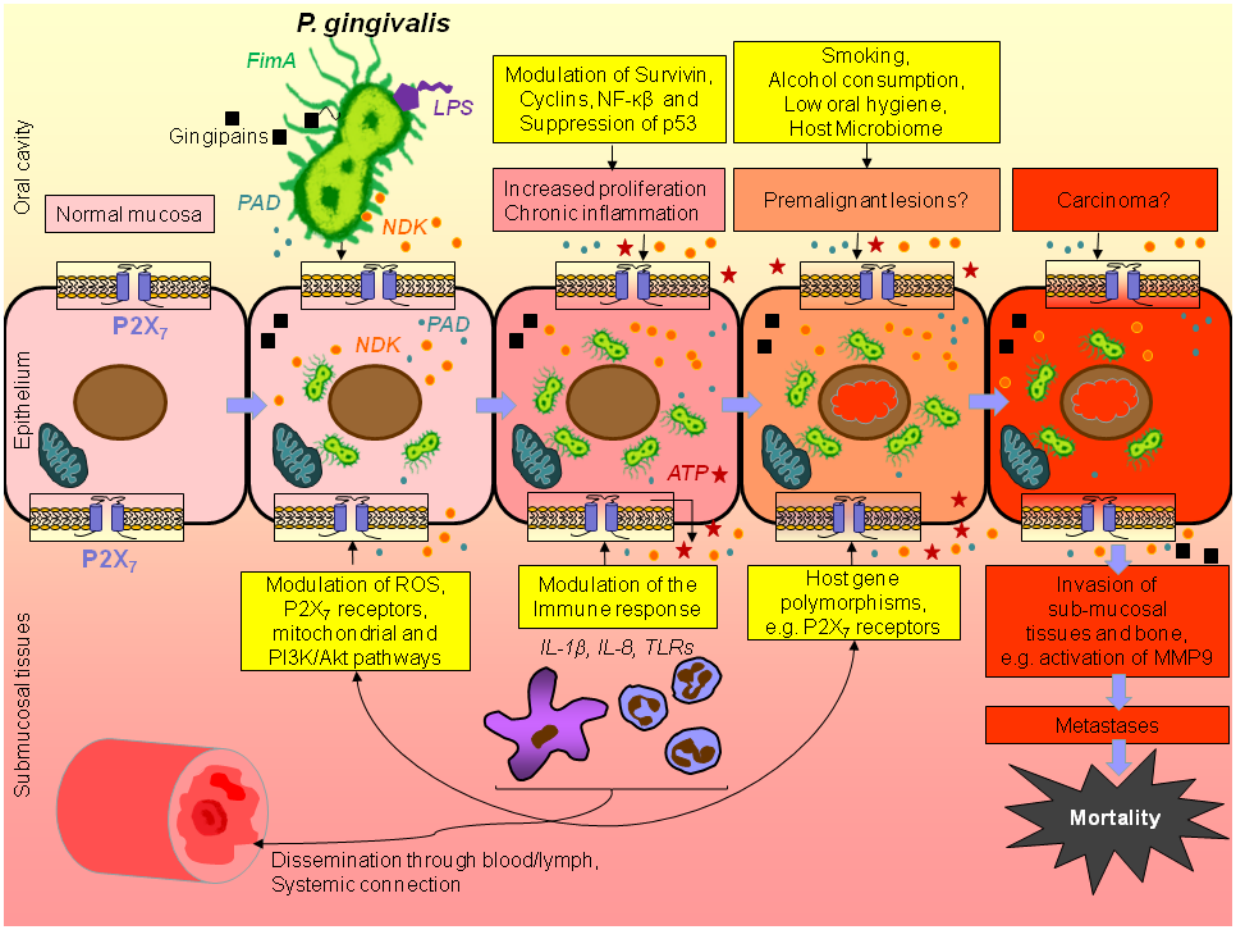


**Figure 2.**

Postulated pro-cancer molecular circuitry of *P. gingivalis* and OECs interface that may affect the increased risk of orodigestive cancers and their poor prognosis. Over the period of its co-evolution with human oral mucosa, *P. gingivalis* has established multiple virulence factors such as distinctive fimbriae (FimA), cysteine proteases (gingipains), lipopolysaccharide (LPS), peptidyl-arginine deiminase (PAD), and nucleoside diphosphate kinase (NDK). These molecules, in concert with genetic predisposition, behavioral factors and possibly in synergy with other microbiome components, can elicit multiple pro-survival effects on the epithelial cells that may lead to predisposition for the cancerous transformation. Additionally, gingipains are suggested to play a role in the activation of MMPs, particularly MMP9, which are shown be associated in the metastatic dissemination of carcinoma cells.