The Implication of ATP Scavenging Behaviour and Upregulation of Immune Regulatory Receptor by Intracellular Porphyromonas gingivalis Based on In-Vitro Models on the Prognosis of Digestive Tract Cancers Regarding the Oral Cancer Patients

Manosha Perera * and Irosha Perera

Posted Date: 25 April 2023

doi: 10.20944/preprints202304.0892.v1

Keywords: Porphyromonas gingivalis; ATP scavenging behavior; Microbiome Medicine; Digestive tract cancers

Communication

The Implication of ATP Scavenging Behaviour and Upregulation of Immune Regulatory Receptor by Intracellular *Porphyromonas gingivalis* Based on In-Vitro Models on the Prognosis of Digestive Tract Cancers Regarding the Oral Cancer Patients

Manosha Lakmali Perera [1,*,†] and Irosha Rukmali Perera [2]

[1] School of Dentistry and Oral Health, Griffith University, Queensland, Australia (Alumni); Irosha_rukmali@yahoo.com
[2] Preventive Oral Health Unit, The National Dental Hospital (Teaching), Colombo, Sri Lanka
* Correspondence: manosha.perera@alumni.griffithuni.edu.au

Abstract: At present there is a huge demand for experimental periodontal models to expand the knowledge in periodontal health related to Microbiome Medicine. Thus far none of the periodontal pathogens or cocktail of pathogens reported as aetiological agents of infectious chronic periodontitis to link with oral squamous cell carcinoma as the way *Helicobactor pyroli* linked with gastric carcinoma and other related gastric malignancies. Nevertheless, invasive pathogenic mechanisms of virulent strains of Porphyromonas gingivalis and Fusobacterium nucleatum singly as well as a duo demonstrated the progression and devastation of oral, pancreatic, and colorectal cancers in different study populations. Periodontal disease may be an inevitable consequence or complication of oral cancer patients who comprise a section of digestive tract cancers, due to suboptimal or poor oral hygiene practices due to unbearable pain and other complications of stage four oral cancer. Periodontitis is a reversible oral condition when it is treated properly at the correct stage and good oral hygiene practices and treating chronic periodontitis showed successful interventions in the prognosis of oral cancer. In the light of these scientifically proven epidemiological, laboratory, and clinical evidence this communication highlights the implication of ATP scavenging behavior and upregulation of immune regulatory receptors by intracellular *Porphyromonas gingivalis* based on in-vitro models on the prognosis of digestive tract cancers regarding the oral cancer patients.

Keywords: *Porphyromonas gingivalis*; ATP scavenging behavior; Microbiome Medicine; Digestive tract cancers

Introduction

Essentially pathogenic bacteria are infectious and aetiological agents of communicable diseses. In contrast, opportunistic bacteria are usually pathogenic when they get the opportunity to abuse the host's immunosuppressive status. Biomedical researcher obtains a breath of experiences when researching the direct influence of infectious and opportunistically harmful biological agents and their products causing DNA mutations [1]. which may be carcinogenic [2] or indirect contribution of these infectious agents manipulating the host's immune system via chronic inflammation [1,3]. In the light of multi-disciplinary research boosting intellectual training with specific emphasis on basic cancer research updates might underpin clinical diagnosis or prognosis outcomes of oncologists' responsibilities and duties in the era of personalized and précised medicine. It is a great investment for scientists who struggle to critically evaluate the applications of research findings to update and upgrade medical protocols either to improve the satisfaction and quality of life of patients or to

achieve goals and annual targets of health care providers. To the best of our knowledge, neither periodontal pathogen can produce a toxin that can damage DNA directly [1,3,4], disrupt the systems that maintain genomic integrity, or stress cells in other ways that indirectly impair the fidelity of DNA replication and repair to be mutagenic in the oral epithelium as in the case of *E. coli* associated colorectal cancers [2]. There is substantial epidemiological evidence of the association of periodontitis with an increased risk of oral cancer [3]. To the best of our knowledge, the carcinogenic attributes of *P. gingivalis*-based on laboratory experiments were able to demonstrate 1st three out of six core hallmarks of cancer proposed by Hanahan and colleagues in 2000 [5], cancerous ffeatures temprorary induced by internalized *P. gingivalis*. Cell internalization [6] is possible with this this one of the three red complex members, due to the invasive ability of *P. gingivalis* strains to thrive well in a secured nutrition-rich niche, whether in a gingival epithelial cell [7] periodontium or neoplastic cell in tumor microenvironment avoiding immune surveillance and immune elimination [8]. On one hand, inhibition of apoptosis by internalized *P. gingivalis* in gingival epithelial cells is identified as one of its molecular pathogenic mechanisms [1,3]. On the other hand, conferring to *P. gingivalis* infected squamous carcinoma cells to upregulate immune regulatory receptors on is considered as a carcinogenic property [9] of this keystone periodontal pathogen [8], which may facilitate the carcinogenesis.

In light of these laboratory findings, it is important to update existing protocols on the preparation of a cancer patient for surgery, radiotherapy, or chemotherapy aiming for better prognostic outcomes. Hence, this perspective highlights the importance of treating infectious bacterial agents to prevent adverse effects on prognosis. Hence, prescribing antibiotics, mouthwash, scaling, and other oral hygiene improvement measures to eradicate the adverse effects of *P.gingivalis* due to chronic periodontitis in digestive tract cancer patients.

P. gingivalis as a Key Stone Pathogen of Chronic Periodontitis

This bacterium reputed as a keystone pathogen in adult periodontitis [10] forms black-pigmented colonies on horse blood agar due to the aggregation of heam on its cell surface [11]. This asaccharolytic, proteolytic strict anaerobe is mainly based on the fermentation of amino acid as the availability of sugar is less in a deep periodontal pocket where this obligate anaerobe thrives well [12].

Gram-negative, *P. gingivalis* represents the 'red complex' of periodontal pathogens with *Tannerella forsythia* and *Treponema denticola*. [13–15]. This species possesses several virulence factors, including cysteine proteinases (gingipains), lipopolysaccharide (LPS), capsule, and fimbriae [8]. In healthy conditions, other members in the subgingival biofilm communities, keep these opportunistic pathogens under control with competition and antagonism for attachment sites and nutrition as well as influencing the host immune system to maintain a *homeostasis/equilibrium* in the immunological and metabolic status of the host. Hence, these pathobiont are not in a position to enrich the periodontium or the tissues, inhibiting the commensals [18]. This equilibrium can be lost, resulting *in dysbiosis* due to various factors which can impart ecological stress on these microbes [1]. These factors consisted of poor oral hygiene due to insufficient tooth cleaning habits, smoking, betel quid chewing, areca nut consumption, diabetes, hormonal changes, medication, and genetic susceptibility [19]. There is a notion that *P. gingivalis* is capable of subverting defense mechanisms by cross-talking with vulnerable hosts under immune suppression. Thus, no wonder to observe a strong correlation between periodontal diseases with systemic diseases–cardiovascular diseases, rheumatoid arthritis, and oro-digestive track cancers in several epidemiological studies [20]. which also makes a bi-directional link between this polymicrobial oral disease with non-communicable diseases of inflammatory origin even in digestive tract cancers thus found in extra-oral sites [21–24] due to the migration ability of this bacterium from subgingival plaque. or supra gingival biofilm [25].

Pathogenic Molecular Mechanisms of *P. gingivalis* as an Aetiological Agent of Opportunistic Infections

Periodontal diseases are a group of infections involving supporting tissues, the periodontium of the teeth. Hence aggressiveness of this gum disease from mild and reversible inflammation of the gingival gum (gingivitis) to chronic destruction of the gingiva, periodontal ligament, and alveolar bone loss resulting in exfoliation of teeth [25]. These clinical outcomes are due to the pathogenic mechanisms [25] of these invasive and evasive [26] keystone periodontal pathogens manipulating the cellular physiology and immunology of the host for their nourishment and flourishment [25]. Entry into the host in sufficient numbers, survival in the hostile environment, propagation and multiplication, Attachment to the complementary host cell receptors by colonization and adhesion, invasion, internalization in specific cells of the organ or system, evasion from immune elimination and causing inflammatory necrotic infections [27] are the hall marks of pathogenic molecular mechanisms of a primary pathogen [28,29].

Molecular mechanisms of pathogenicity of an opportunistic pathogen or pathobiont are short of the first two steps of eight hallmarks proposed for any primary or opportunistic pathogen. Thus, enter into the host in sufficient numbers, survival in the hostile environment is not applicable for this member in subgingival flora, and elevation of numbers of this red complex companion usually occurs in immunosuppressive disease conditions [26] which is also considered as predisposing factors [30] of periodontitis and due to inadequate oral hygiene practices [31]. Initial colonization of *P. gingivalis* in children is found to be transmitted from infected individuals [32] either elderly caretakers or parents. Transmission via saliva among spouses is also possible but identifying the common source was impossible due to the presence of different genotypes among individuals [25]. This may be due to the selective proliferation of the most robust phenotypes or strains of the same species to facilitate the 'survival of the fittest' eliminating the sensitive phenotypes. Though heterotrophic bacteria are the most versatile organisms to adapt according to the adversities of their hosts or environment [31] applicability of this hypothesis for genotypic variations even among related individuals warrants properly planned laboratory investigations minimizing errors due to chance, bias, and confounders.

Cell Internalization Is One of the Virulence Mechanisms of *P. gingivalis*

Invasive pathogens evolved for survival and replication as residential pathogens. The internalization process needs to facilitate by the host cell, where the pathogen, adhered to the complementary surface receptors using specific adhesins [32]. The nonmalignant host cell types in which pathogens can thrive include epithelial, endothelial, macrophages, and neutrophils [33]. The ability to replication of ingested pathogens is by acting against destruction mechanisms using the host vesicle trafficking pathway. The resilience mechanisms of phagocyte resident bacteria started revealing and redirection [34,35].

Few tissue culture models have been used to elucidate the cell internalization of major pathogens; *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Fusobacterium nucleatum*, *Prevotella intermedia*, and *Tannerella forsythia.Among them, P. gingivalis* is the most studied oral pathogen. Different tissue culture models have been usedto study the cell internalization process. The residential ability or cell internalization characteristic of *P.gingivalis* strains reflects the ability to persist in a local niche subverting the host's innate immune mechanisms [36,37]. According to genotyping results, there is a marked genetic variation and virulence potential of different strains in the same species of *P. gingivalis* [38]. Thus, the virulence potential of *P. gingivalis* strains seemed to acquire by exchanging bacterial DNA among them [39]. Close physical contact between the bacterium and the host cell receptors is a prerequisite for the cell internalization process [39]. The interaction of P. gingivalis FimA fimbriae with epithelial cell surface integrins, originates a cellular response that recruits FAK and paxillin to the cytoplasmic membrane at the bacterial attachment site [40,41]. Subsequently, interactions among integrin, FAK, and paxillin make a phosphorylation-regulated signaling scaffold that activates Rho-family GTPases, enzymes that play a vital role in starting downstream signaling cascades and regulating cytoskeletal dynamics [42.43]. Then, the recruitment of lipid raft components, and host-cell phosphorylation termed actin and microtubule

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 25 April 2023 doi:10.20944/preprints202304.0892.v1

remodeling, activity is all needed for the internalization of *P. gingivalis* [44,45]. This cell internalization process takes approximately 15 min resulting in the perinuclear localization of the bacteria [46].

ATP Scavenging Behavior of Intracellular *P. gingivalis* to Inhibit Apoptosis

Apoptosis is the genetically determined programmed cell death in somatic and immune cells [47]. This process is critical in the growth and function of a human comprising trillions of different types of cells.

Several virulence factors are reported to be involved in the direct activation of inflammation and gingival cell proliferation mediated by *P. gingivalis*. Among them, a homolog of nucleoside diphosphate kinase (NDK), is an ATP-consuming enzyme, secreted extracellularly [16]. The P2X7 receptor (P2X7R) is expressed in different types of cells including neurons, macrophages, dendritic and microglial cells, fibroblasts, lymphocytes, endothelial cells, and gingival epithelial cells (GEC). This receptor has gained attention as an important multi-level mediator in controlling intracellular infections by regulating the innate immune response, apoptosis, intracellular trafficking, and generation of reactive oxygen species (ROS) [48]. These multi-functions reflect the importance of (P2X7R) not only in cell death but also in cell survival. These two contradictory functions are dependent on two specific pathways, both are activated by the same P2X7R but diverse phases of the cell cycle. Low tonic activation of P2X7R inhibits apoptosis and renders cell growth. In contrast, enormous P2X7R leads to programmed cell death/apoptosis [16]. Moreover, extracellular ATP ligation on P2X7R is necessary for the activation of the Caspase 3/7 apoptotic pathway for programmed cell death/apoptosis. Thus, high concentrations of ATP induce membrane blebbing is considered a hallmark of apoptosis.

Laboratory evidence based on *P. gingivalis* infected epithelial cells (GEC) demonstrated that the NDK secretes by *P. gingivalis* converts ATP into ADP, inhibiting the ligation of ATP with P2X7 receptors. Subsequently, preventing the ATP-induced Caspase 3/7 apoptotic pathway in gingival epithelial cells [16]. In contrast, an *end-deficient* mutant was unable to prevent ATP-induced apoptosis in gingival epithelial cells (GEC) in the same experiment [16].

Upregulation of Immune Regulatory Receptor on Squamous Carcinoma Cells by Intracellular *Porphyromonas gingivalis*

Interestingly, laboratory evidence based on tissue culture and animal model experiment provide internalized *P.gingivalis* detected using immunofluorescent/confocal microscopy, floresecence in situ hybridization (FISH), Immunohistochemistry (IHC), IHC, IHC/FISH in colorectal cancer cells(CRC) [49], pancreatic cell lines [50], eosophageal cancer [51] and chemically oral cancer induced murine model [52] respectively.

Accordingly, the mportant finding of upregulation of the immune-regulatory receptor PD-L1 (B7-H1) in *P.gingivalis* infected oral squamous carcinoma cells and gingival epithelial cell [53]. Expression of B7 homolog 1 (B7-H1) receptors rises in most human cancers causing anergy and apoptosis of activated T cells. The B7-H1 receptors are upregulated on cancer/transformed cells, and the B7-H1 receptors. The B7-H1 receptors found to be upregulated on cancer/transformed cells. Then these receptors seemed blocking the PD1 receptors on tumor-infiltrating lymphocytes (TILS) [24]. Hence, it is justifiable to hypothesis that the upregulation of B7 homolog 1 (B7-H1) receptors may provide survival of cancerous acting against cytotoxic activity of natural killer (NK) cells, in addition to immune evasion of tumours using immune check points. This hypothesis needs further investigations with suitable animal model.

The Implication of Intracellular *Porphyromonas gingivalis* Based on In-Vitro Models on the Prognosis of Digestive Tract Cancers Regarding the Oral Cancer Patients

Establishment of *P. gingivalis* as an oncogenic bacterium based on the findings of invitro and invivo models, seems a fishing expedition due to the fact that most investigators did not pay the attention to set up these experients getting rid of the *bias* introduced by the establishment of *Helicobacter pylori* as the aetiological agent of gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphomas [55]. To this date, noone has conducted a systematic review on carcinogenic mechanisms of *P. gingivalis* in vitro and invivo experiments. All authors of scooping and narrative review on Possible role of *P. gingivalis* in oral, orodigestive, pancreatic and colorectal cancers operated in silos. They have not embraced the holistic approach of connecting all of these attributes as pathogenic or virulent mechanisms that are being used for thriving in resident state in protein enriched and vascularized neoplastic cells for this proteolytic bacterium which also demonstrates an affinity to haem component.

Oral hygiene improvement before treatment modalities for oral cancer is an established practice in oro-maxillo facial (OMF) units in Sri Lanka. This key stone periodontal pathogen is been able to survive in tumour micro environment using amazing stratergies to thrive well escaping from immune surveillance mechanisms and immune elimination in tumour micro environment. This communication concluded by suggesting including oral hygiene improvement in standard management protocols and guidelines of oncology patients by referring those patients to hospital dental clinics before commencing the treatment modalities for oesophageal, pancreatic, and colorectal cancers depending on the laboratory experiments based on the epidemiological finding of *P. gingivalis* in an extra-oral site of digestive cancers.

Conflicts of Interest: The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

References

1. Perera, M.; et al. Emerging role of bacteria in oral carcinogenesis: A review with special reference to perio-pathogenic bacteria. *J. Oral Microbiol.* **2016**, *8*, 32762.
2. Elagan, S.K.; et al. Role of bacteria in the incidence of Common GIT cancers: The dialectical role of integrated bacterial DNA in human carcinogenesis. *Infect. Drug Resist.* **2021**, *14*, 2003–2014.
3. Al-Hebshi, N.N.; et al. The microbiome of oral squamous cell carcinomas: A functional perspective. *Curr. Oral Health Rep.* **2019**, *6*, 145–160.
4. Wu, J.; et al. Porphyromonas gingivalis promotes 4-nitroquinoline -1 –oxide induced oral carcinogenesis with an alteration of fatty acid metabolism. *Front. Microbiol.* **2018**, *9*, 2081.
5. Hanahan, D.; Weinberg, R.A. The hallmarks of cancer. *Cell* **2000**, *100*, 57–70.
6. Lamont, R.J.; Chan, A.; Belton, C.M.; Izutsu, K.T.; Vasel, D.; Weinberg, A. Porphyromonas gingivalis invasion of gingival epithelial cells. *Infect. Immun.* **1995**, *63*, 3878–3885.
7. Lamont, R.J.; Oda, D.; Persson, R.E.; Persson, G.R. Interaction of Porphyromonas gingivalis with gingival epithelial cells maintained in culture. *Oral Microbiol. Immunol.* **1992**, *7*, 364–367.
8. Lamont, R.J.; Jenkinson, H.F. Life Below the Gum Line: Pathogenic Mechanisms of Porphyromonas gingivalis. *Microbiol. Mol. Biol. Rev.* **1998**, *62*, 1244–1263.
9. Sun, Z.; Xiong, C.; Teh, S.W.; Lim, J.C.W.; Kumar, S.; Thilakavathy, K. Mechanisms of Oral Bacterial Virulence Factors in Pancreatic Cancer. *Front. Cell. Infect. Microbiol.* **2019**, *9*, 412.
10. Hajishengallis, G.; Lamont, R.J. Dancing with the stars: How choreographed bacterial interactions dictate nososymbiocy and give rise to keystone pathogens, accessory pathogens, and pathobionts. *Trends Microbiol.* **2016**, *24*, 477–489.
11. How, K.Y.; Song, K.P.; Chan, K.G. Porphyromonas gingivalis: An Overview of Periodontopathic Pathogen below the Gum Line. *Front. Microbiol.* **2016**, *7*, 53. https://doi.org/10.3389/fmicb.2016.00053.
12. Bostanci, N.; Thurnheer, T.; Aduse-Opoku, J.; Curtis, M.A.; Zinkernagel, A.S.; Belibasakis, G.N. Porphyromonas gingivalis regulates TREM-1 in human polymorphonuclear neutrophils via its gingipains. *PLoS ONE* **2013**, *8*, e75784. https://doi.org/10.1371/journal.pone.0075784.

13. Lamont, R.J.; Hajishengallis, G. Polymicrobial synergy and dysbiosis in inflammatory disease. *Trends Mol. Med.* **2015**, *21*, 172–183.
14. Hajishengallis, G.; Lamont, R.J. Breaking bad: Manipulation of the host response by Porphyromonas gingivalis. *Eur. J. Immunol.* **2014**, *44*, 328–338.
15. Atanasova, K.R.; Yilmaz, O. Looking in the Porphyromonas gingivalis cabinet of curiosities: The microbium, the host and cancer association. *Mol. Oral Microbiol.* **2014**, *29*, 55–66.
16. Yilmaz, Ö.; et al. ATP scavenging by the intracellular pathogen Porphyromonas gingivalis inhibits P2X7-mediated host-cell apoptosis. *Cell. Microbiol.* **2008**, *10*, 863–875.
17. Al-Hebshi, N.N.; Borgnakke, W.S.; Johnson, N.W. The microbiome of oral squamous cell carcinomas: A functional perspective. *Curr. Oral Health Rep.* **2019**, *6*, 145–160.
18. Lamont, R.J.; Hajishengallis, G. Polymicrobial synergy and dysbiosis in inflammatory disease. *Trends Mol. Med.* **2015**, *21*, 172–183.
19. Kilian, M.; et al. The oral microbiome–an update for oral healthcare professionals. *Br. Dent. J.* **2016**, *221*, 657.
20. Hoare, A.; et al. Chronic inflammation as a link between periodontitis and carcinogenesis. *Mediat. Inflamm.* **2019**.
21. Perera, M.; Al-hebshi, N.N.; Perera, I.; Ipe, D.; Ulett, G.C.; Speicher, D.J.; Chen, T.; Johnson, N.W. Inflammatory bacteriome and oral squamous cell carcinoma. *J. Dent. Res.* **2018**, *97*, 725–732.
22. Al-hebshi, N.N.; Nasher, A.T.; Maryoud, M.Y.; Homeida, H.E.; Chen, T.; Idris, A.M.; Johnson., N.W. "Inflammatory bacteriome featuring Fusobacterium nucleatum and Pseudomonas aeruginosa identified in association with oral squamous cell carcinoma. *Sci. Rep.* **2017**, *7*, 1–10.
23. Sheflin, A.M.; Whitney, A.K.; Weir, T.L. Cancer-promoting effects of microbial dysbiosis. *Curr. Oncol. Rep.* **2014**, *16*, 406.
24. Olsen, I.; Yilmaz, Ö. Possible role of *Porphyromonas gingivalis* in orodigestive cancers. *J. Oral Microbiol.* **2019**, *11*, 1563410. https://doi.org/10.1080/20002297.2018.1563410.
25. Lamont, R.J.; Jenkinson, H.F. Life Below the Gum Line: Pathogenic Mechanisms of Porphyromonas gingivalis. *Microbiol. Mol. Biol. Rev.* **1998**, *62*, 1244–1263.
26. Bostanci, N.; Belibasakis, G.N. Porphyromonas gingivalis: An invasive and evasive opportunistic oral pathogen. *FEMS Microbiol. Lett.* **2012**, *333*, 1–9.
27. Hajishengallis, G.; Liang, S.; Payne, M.A.; et al. Low-abundance biofilm species orchestrates inflammatory periodontal disease through the commensal microbiota and complement. *Cell Host Microbe* **2011**, *10*, 497–506.
28. Wilson, J.W.; Schurr, M.J.; LeBlanc, C.L.; Ramamurthy, R.; Buchanan, K.L.; Nickerson, C.A. Mechanisms of bacterial pathogenicity. *Postgrad. Med. J.* **2002**, *78*, 216–224.
29. Finlay, B.B.; Falkow, S. Common themes in microbial pathogenicity revisited. *Microbiol. Mol. Biol. Rev.* **1997**, *61*, 136–169.
30. Perera, M. The Microbiome profile of oral squamous cell carcinoma tissues in a group of Sri Lankan male patients. https://doi.org/10.25904/1912/3833.
31. Perera, L.; Perera, I. Revisiting For Resolving. The Ecological Perspective of Periodontal Bacteriome for Prevention and Control of Periodontitis in COVID-19 Era. *J. Dental. Sci.* **2020**, *5*, 000275.
32. Greenstein, G.; Lamster, I. Bacterial transmission in periodontal diseases: A critical review. *J. Periodontol.* **1997**, *68*, 421–431.
33. Wilson, J.W.; Schurr, M.J.; LeBlane, C.L.; et al. Mechanisms of bacterial pathogenicity. *Postgrad. Med. J.* **2002**, *78*, 216–224.
34. Hackstadt, T. Redirection of host vesicle trafficking pathways by intracellular parasites. *Traffic* **2000**, *1*, 93–99.
35. Russell, D. Where to stay inside the cell: A homesteader's guide to intracellular parasitism. In *Cellular Microbiology*; Cossart, P., Boquet, P., Normark, S., Eds.; ASM Press: Washington, DC, USA, 2000.
36. Hajishengallis, G. Porphyromonas gingivalis–host interactions: Open war or intelligent guerilla tactics? *Microbes Infect* **2009**, *11*, 637–645.
37. Hajishengallis, G.; Lambris, J.D. Microbial manipulation of receptor crosstalk in innate immunity. *Nat. Rev. Immunol.* **2011**, *11*, 187–200.
38. Menard, C.; Mouton, C. Clonal diversity of the taxon Porphyromonas gingivalis assessed by random amplified polymorphic DNA fingerprinting. *Infect Immun.* **1995**, *63*, 2522–2531.

39. Tribble, G.D.; Lamont, R.J. Bacterial invasion of epithelial cells and spreading in periodontal tissue. *Periodontol 2000* **2010**, *52*, 68–83. https://doi.org/10.1111/j.1600-0757.2009.00323.x.
40. Yilmaz, O.; Watanabe, K.; Lamont, R.J. Involvement of integrins in fimbriae-mediated binding and invasion by Porphyromonas gingivalis. *Cell Microbiol.* **2002**, *4*, 305–314.
41. Yilmaz, O.; Young, P.A.; Lamont, R.J.; Kenny, G.E. Gingival epithelial cell signalling and cytoskeletal responses to Porphyromonas gingivalis invasion. *Microbiology* **2003**, *149*, 2417–2426.
42. Deakin, N.O.; Turner, C.E. Paxillin comes of age. *J. Cell Sci.* **2008**, *121 (Pt 15)*, 2435.
43. Harburger, D.S.; Calderwood, D.A. Integrin signalling at a glance. *J. Cell Sci.* 2009, *122 (Pt 2)*, 159.
44. Watanabe, K.; Yilmaz, O.; Nakhjiri, S.F.; Belton, C.M.; Lamont, R.J. Association of mitogen-activated protein kinase pathways with gingival epithelial cell responses to Porphyromonas gingivalis infection. *Infect. Immun.* **2001**, *69*, 6731–6737.
45. Yilmaz, O.; Young, P.A.; Lamont, R.J.; Kenny, G.E. Gingival epithelial cell signalling and cytoskeletal responses to Porphyromonas gingivalis invasion. *Microbiology* **2003**, *149*, 2417–2426.
46. Belton, C.M.; Izutsu, K.T.; Goodwin, P.C.; Park, Y.; Lamont, R.J. Fluorescence image analysis of the association between Porphyromonas gingivalis and gingival epithelial cells. *Cell Microbiol.* **1999**, *1*, 215–223.
47. Susin, S.A.; Daugas, E.; Ravagnan, L.; Samejima, K.; Zamzami, N.; Loeffler, M.; Costantini, P.; Ferri, K.F.; Irinopoulou, T.; Prevost, M.C.; et al. Two distinct pathways leading to nuclear apoptosis. *J. Exp. Med.* **2000**, *192*, 571–580.
48. Choi, C.H.; et al. P orphyromonas gingivalis-nucleoside-diphosphate-kinase inhibits ATP-induced reactive-oxygen-species via P2X7 receptor/NADPH-oxidase signalling and contributes to persistence. *Cell. Microbiol.* **2013**, *15*, 961–976.
49. Mu, W.; Jia, Y.; Chen, X.; Li, H.; Wang, Z.; Cheng, B. Intracellular *Porphyromonas gingivalis* Promotes the Proliferation of Colorectal Cancer Cells via the MAPK/ERK Signaling Pathway. *Front. Cell. Infect. Microbiol.* **2020**, *10*, 584798. https://doi.org/10.3389/fcimb.2020.584798.
50. Gnanasekaran, J.; Binder Gallimidi, A.; Saba, E.; Pandi, K.; Eli Berchoer, L.; Hermano, E.; Angabo, S.; Makkawi, H.A.; Khashan, A.; Daoud, A.; et al. Intracellular *Porphyromonas gingivalis* Promotes the Tumorigenic Behavior of Pancreatic Carcinoma Cells. *Cancers* **2020**, *12*, 2331. https://doi.org/10.3390/cancers12082331.
51. Gao, S.; Li, S.; Ma, Z.; et al. Presence of *Porphyromonas gingivalis* in esophagus and its association with the clinicopathological characteristics and survival in patients with esophageal cancer. *Infect. Agents Cancer* **2016**, *11*, 3. https://doi.org/10.1186/s13027-016-0049-x.
52. Wen, L.; Mu, W.; Lu, H.; Wang, X.; Fang, J.; Jia, Y.; Li, Q.; Wang, D.; Wen, S.; Guo, J.; et al. *Porphyromonas gingivalis* Promotes Oral Squamous Cell Carcinoma Progression in an Immune Microenvironment. *J. Dent. Res.* **2020**, *99*, 666–675. https://doi.org/10.1177/0022034520909312.
53. Groeger, S.; Jarzina, F.; Mamat, U.; et al. Induction of B7-H1 receptor by bacterial cells fractions of Porphyromonas gingivalis on human oral epithelial cells: B7-H1 induction by Porphyromonas gingivalis fractions. *Immunobiology* **2017**, *222*, 137–147.
54. Groeger, S.; Domann, E.; Gonzales, J.R.; et al. B7-H1 and B7-DC receptors of oral squamous carcinoma cells are upregulated by Porphyromonas gingivalis. *Immunobiology* **2011**, *216*, 1302–1310.
55. Mager, D. Bacteria and cancer: Cause, coincidence or cure? A review. *J. Transl. Med.* **2006**, *4*, 14.