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AIMS AND SCOPE

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RESPONSIBLE EDITORS FOR THIS ISSUE

Porphyromonas gingivalis and digestive system cancers

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Abstract

Porphyromonas gingivalis (*P. gingivalis*) is an anaerobic gram-negative bacterium that colonizes in the epithelium and has been strongly associated with periodontal disease. Recently, various degrees of associations between *P. gingivalis* and digestive system cancers, including oral squamous cell carcinoma in the oral cavity, oesophageal squamous carcinoma in the digestive tract, and pancreatic cancer in pancreatic tissues, have been displayed in multiple clinical and experimental studies. Since *P. gingivalis* has a strong association with periodontal diseases, not only the relationships between *P. gingivalis* and digestive system tumours but also the effects induced by periodontal diseases on cancers are well-illustrated in this review. In addition, the prevention and possible treatments for these digestive system tumours induced by *P. gingivalis* infection are also included in this review. At the end, we also highlighted the possible mechanisms of cancers caused by *P. gingivalis*. One important carcinogenic effect of *P. gingivalis* is inhibiting the apoptosis of epithelial cells, which also plays an intrinsic role in protecting cancerous cells. Some signalling pathways activated by *P. gingivalis* are involved in cell apoptosis, tumourigenesis, immune evasion and cell invasion of tumour cells. In addition, metabolism of potentially carcinogenic substances caused by *P. gingivalis* is also one of the connections between this bacterium and cancers.

Key words: *Porphyromonas gingivalis*; Oral squamous cell carcinoma; Oesophageal squamous cell carcinoma; Pancreatic cancer; Periodontal diseases

Core tip: *Porphyromonas gingivalis* (*P. gingivalis*) has been discovered in many digestive system cancers, such as oral squamous cell carcinoma, oesophageal squamous cell carcinoma, and pancreatic cancer. For the strong association between *P. gingivalis* and periodontal diseases, we also interpret how periodontal diseases push effects on digestive system tumours. This review also presents some preventions and possible treatments for these cancers associated with *P. gingivalis* infection. In addition, the mechanisms by

which *P. gingivalis* affects the occurrence and development of carcinomas are covered, including immune evasion, tumourigenesis, inhibition of apoptosis and invasion of tumour cells.

INTRODUCTION

Porphyromonas gingivalis (*P. gingivalis*), one of several hundred bacterial species in the oral cavity, is an anaerobic gram-negative bacterium[1] and is highly associated with periodontal diseases[2]. Dental plaque is a biofilm on the surface of teeth[3] and functions as a highly organized and integrated microbial community in the mouth[4]. *P. gingivalis* is part of the composition of dental plaque and endows dental plaque with a panoply of critical virulence attributes[5]. This bacterium regulates the immune reaction of host to promote the proliferation of microbial biofilm, thereby destroying the homeostasis of the host and causing biological disorders and disease[6]. *P. gingivalis* can be found in the gingival epithelium[7]. To effectively colonize, *P. gingivalis* secretes protein adhesins, heminbinding proteins and proteinases. Such factors could cause toxicity as well[8-10]. Arg-specific gingipains (RgpA and RgpB) and Lys-specific gingipain (Kgp) are cysteine proteinases, which are extracellular proteases with multiple effects on both the innate and adaptive immune responses[11,12]. These cysteine proteinases are capable of degrading extensive connective tissues and large host defence molecules[13,14]. The R-gingipains (Rgp) and Kgp are demonstrated highly related to the relief of inflammation and host defence evasion by means of activating kinin cascade and liquid phase transformation of complement C3 and C5 proteins[15,16]. Apart from these defences, some other factors, such as fimbriae, haemagglutinins, lipopolysaccharide, capsule polysaccharides, and major outer membrane protein, have also been demonstrated for potential virulence[17,18]. Recently, an increasing number of investigations have focused on cancers related to *P. gingivalis*. With the deepening of the research concerning this bacterium, outer membrane protein has been reported to make contributions to the interaction and colonization of host, the evasion of immune defense, as well as the destruction of periodontal tissues[19], which may explain how *P. gingivalis* pushes impacts on several digestive cancers. However, more and complicated internal mechanisms still need to be uncovered. This article aims to review the current relationship between *P. gingivalis* and cancer.

P. GINGIVALIS AND ORAL CANCER

Oral cavity consists of diverse boundary surfaces, such as the gingiva, the back of the tongue, tongue side, oral mucosa and so on which contribute to the colonization and growth of various microorganisms. In 2016, accompanying an approximate 48330 new diagnoses and 9570 deaths, oral cancer was considered the sixth most common carcinoma globally[20]. Among these, what most commonly happened in oral cavity is oral squamous cell carcinoma (OSCC)[21]. *P. gingivalis* has been discovered colonizing in periodontium and spreading in the original lesion locations of OSCC as well, such as oral and lingual mucosa[22]. It is well known that tobacco and alcohol are the major risk factors for oral cancer, and approximately three-fourths of all oral and pharyngeal cancers are owing to tobacco smoking and alcohol drinking in the United States[23]. Upon alcohol drinking, *P. gingivalis* would dehydrogenate ethanol to acetaldehyde, which is a carcinogenic derivative and capable of contributing to DNA damage, mutation and excessive proliferation of the epithelium[24,25].

The concentration rate of *P. gingivalis* was discovered to be higher among cancer cells than normal tissues of the mouth by Katz *et al*[26] in 2011. Meanwhile, these authors suggested that *P. gingivalis* may lead to mouth cancer and the induction of epithelial cell transformation into a tumour. In a meta-analysis, the prevalence of *P. gingivalis* was 40.7%, and *P. gingivalis* made the chances of cancer and periodontal disease increasing 1.36 times[27]. Kang *et al*[28]'s study also showed that the incidence of *P. gingivalis* in patients with head and neck cancer and in healthy subjects is

significantly different. Besides, compared to non-infected with *P. gingivalis* controls, those with long-term infection showed the up-regulating expressions of CD44 and CD133 which are the well-known cancer stem cell markers, and promoted the tumorigenic properties[29]. By activating ERK1/2-Ets1, p38/HSP27, and PAR2/NF-kB pathways, *P. gingivalis* increases pro-matrix metalloproteinase-9 (proMMP-9) levels and consequently promotes cellular invasion of OSCC cell lines when the proenzyme is stimulated by gingipains[30]. Comparing to uninfected cells, those infected with *P. gingivalis* cells were monitored to increase MMP-1, -2, -9 and -10 levels in time dependence[31]. In addition, activated MMP-9 has been illustrated to enhance the invasion of tumour cells; this study was performed with the help of a specific anti-MMP-9 blocking monoclonal antibody[32]. As Ha *et al*[33]'s findings also suggested, *P. gingivalis* infection makes significant functions in promoting the invasion of OSCC cells, including SCC-25, OSC-20 and SAS cells, through upregulating levels of IL-8 and MMPs (particularly MMP-1 and MMP-2). By establishing a long-term model in which human immortalized oral epithelial cells were chronically challenged with *P. gingivalis* for up to 23 wk, Geng *et al*[34] found that long-term exposure to *P. gingivalis* accelerated the cell cycle and promoted cell migration as well as invasion abilities, both of which eventually induced metastatic proliferation in distant organs. Compared with non-infected *P. gingivalis* in mice, it was demonstrated that chronic infection would make the promotion of metastasis *via* the blood pathway *in vivo*[21].

P. GINGIVALIS AND OESOPHAGEAL CANCER

On a global scale, oesophageal cancer, the eighth incidence of tumour also contributes to the sixth highest mortality. Asia, especially Central China, is a high-incidence area, whereas data recently revealed that newly-diagnosed cases are rising in Western Europe and America[35]. Oesophageal cancer is characteristic of difficulty in early diagnosis, rapid development and high mortality. Tobacco smoking and excess alcohol consumption are risk factors for oesophageal cancer[36]. This cancer has two major histological subtypes, squamous cell carcinoma and adenocarcinoma; the former is common in developing countries and the latter is more common in developed nations[37]. In this review, oesophageal squamous cell carcinoma (ESCC) is the focus. The similarity in histology between oesophageal squamous cells and oral squamous cells is well-known, and it has been revealed that there is a high frequency of *P. gingivalis* (61%) in ESCC[36]. In this study, the expression intensity of *P. gingivalis* antigen and the exclusive Lys-gingipain protease, as well as the detection of the *P. gingivalis*-specific 16S rDNA in ESCC patients, all of them were notably higher in tumour tissue than in ambient tissue or normal controls. In addition, the differentiation of tumour cells, the distant metastasis of ESCC, the survival ratio of ESCC patients and other clinicopathological factors all positively relate to the existence of *P. gingivalis*. Such conclusions not only firstly proved that infection with *P. gingivalis* would act as a new risk factor of ESCC, but also indicated that *P. gingivalis* could serve as a prognostic biomarker for ESCC[36]. The inhibition of epithelial cell apoptosis, the promotion of tumour cell immune invasion and the metabolism of potentially carcinogenic substances induced by *P. gingivalis* all contribute to the occurrence and development of ESCC[12,24,25,32,38,39]. Gao *et al*[40] firstly reported the implication between host immunologic reaction to P. gingivalis and malignant proliferation of ESCC cells. They also suggested that IgG and IgA for P. gingivalis played a role as possible serum markers of ESCC, and combining the both would advance the diagnosis and improve prognosis[40]. Finally, interestingly, the rate of infection of P. gingivalis is much higher in oesophageal cancers than in cardiac cancers and is approximately as low as zero in gastric cancer, which is due to lack of acid adaptation[41].

P. GINGIVALIS AND PANCREATIC CANCER

Pancreatic cancer, which has a low frequency, is unexpectedly the fourth leading cause of death among various carcinomas, with an overall five-year survival rate of merely 8.2% (in 2007–2013) for all stages[42,43]. There are several factors leading to a poor prognostic performance of this devastating cancer, such as the deficiency of serum biomarkers for diagnosis and prognosis, the absence of biomarkers which could function as guidelines for individual therapy, and the broad and primary resistance to chemotherapy[43]. The bacterial colony is critical to developing gastrointestinal mucosal immune system, maintaining a normal physiological circumstance, and providing necessary nourishment, which has been of significance

in various disease states[44,45]. Multiple observations have shown that there is an overlap between oral microbiota and digestive tract microbiota partly due to mastication and daily oral hygiene, such as tooth brushing and flossing[42], which promotes multiple avenues for the dissemination of dysbiosis[44]. Furthermore, poor oral health is linked with an increased risk of pancreatic cancer development[46]. Those who suffer from 2 types of periodontitis caused by oral microorganism tend to be subsequent at higher risks of increasing the occurrence of pancreatic cancer[47]. A large European prospective cohort study found that elevated serum antibodies to the ATTC 53978 strain of *P. gingivalis* could triple the risks of pancreatic carcinoma[48]. As Dr Miller recently demonstrated, *P. gingivalis* initiated the Toll-like receptor (TLR) signalling pathways[49], while TLR activation critically contributed to pancreatic carcinogenesis in animal models[50]. This result was considered direct evidence that *P. gingivalis* increases pancreatic cancer development. Additionally, high rates of tumour suppressor gene p53 mutations were detected in pancreatic cancer patients, and it was concluded that abnormality of the p53 gene is a significant event in human pancreatic tumourigenesis[51]. In addition, in the progression of *P. gingivalis* inhibiting epithelial cell apoptosis, p53 can be activated by *P. gingivalis* invasion[52,53]. As a result, mutations in p53 can play a role as a bridge that links *P. gingivalis* with the development of pancreatic cancer, but further investigations are needed to enrich this link.

In summary, *P. gingivalis* may be considered a biomarker in the occurrence and development of pancreatic cancer. It is urgent to conduct more research to explain the mechanism by which *P. gingivalis* acts on pancreatic cancer and to improve the prevention and treatment of pancreatic cancer. Through these studies, it is hopeful to contain the high mortality of pancreatic cancer and release the tense status quo in pancreatic cancer.

PERIODONTAL DISEASE AND CANCERS

Periodontal disease is an inflammation that occurs in gums, which could induce the recession of gum, the damage of soft tissue, and the loss of bone and tooth (severe periodontitis)[54]. The identification of the "red complex", which consists of *Tannerella forsythia*, *P. gingivalis* and *Treponema denticola*, is a major milestone in the research of periodontal microbiology. In terms of esophageal adenocarcinoma risk, *Tannerella forsythia* has to be found increasing this risk, while the exhaustion of *Neisseria* and *Streptococcus pneumoniae* was related to lower risk, and the abundance of *P. gingivalis* tended to increase the risk of ESCC[55]. Among these bacterial species, *P. gingivalis* shows the strongest association with periodontitis[56]. Additionally, *P. gingivalis* acts as an independent risk factor for the above-mentioned cancers. Therefore, we further discuss the relationship between periodontitis and these cancers. Substantial investigations have accumulated evidence supporting that periodontitis causes the host maintain a chronic inflammatory state[57] and confirming that cancer is associated with chronic infections or inflammation[58]. Taking the receptor to advanced glycation end products (RAGE) as an example, which is a multi-ligand receptor that can express on numerous cytomembrane and link with chronic infections, has been suggested to play a role in carcinogenesis[59]. Consequently, we can conclude that periodontitis has direct effects on cancers. As a prospective cohort study revealed, periodontal disease might play the role of being a marker for a susceptible immune system or having a direct impact on cancer risk[60]. Some others also suggested that there are positive connections between periodontitis and several tumours, including pancreatic carcinoma, lung tumours and digestive cancers[61,62]. Tezal *et al*[63] concluded that chronic periodontal disease could function as a risk factor for oral premalignant lesions and cancers. OSCC patients are highly sensitive to chronic periodontitis, which suggests the existence of OSCC cells in a chronic inflammatory state. Since periodontitis is attributed to multiple bacterial pathogens, OSCC patients infected with such inflammation are in consistent exposure to excessive periodontal bacteria[64,65]. These bacterial pathogens may subsequently affect the biological behaviour of oral cancer by modulating inflammatory mediators and invading related molecules[31]. Chronic periodontitis not only affects the occurrence and development of oral cancer but also contributes to the metastasis of this cancer[29,31]. The relationship between periodontitis and pancreatic cancer has also been revealed from a great deal of research. An evidence-based review showed that inflammation plays a key role in pancreatic cancer[66], and in a prospective cohort study of male health, professionals confirmed the strong positive association between periodontal disease and pancreatic cancer. In this cohort study, the existence of periodontal disease increases the risk of pancreatic cancer by 64%[46]. The systemic dissemination of oral microorganism and their toxic substance may also cause systemic inflammation and immune reaction,

which could trigger the incidence of pancreatic cancer[66-68]. However, the role of oral microbiota in the development of pancreatic cancer is still under study. As mentioned in a former section of this review, periodontal disease could induce the loss of a tooth[54]. A prospective study also suggested that tooth loss has increased the incidence of esophageal and gastric cancers, which may owe to the alterations of oral microflora and subsequent increased carcinogens *in vivo*[69,70]. As a result, periodontal disease is connected with such tumours. In addition, the risk of lung tumour has been increased for those who suffering from periodontal disease in cohort studies, which may be because of the aspiration of oral pathogens into the lungs, the modification of the mucosal surface, the destruction of salivary pellicles, and the alteration of the respiratory epithelium[71]. Periodontal disease may establish more connections with other cancers, such as bladder cancer, colorectal cancer and so on, but a large amount of research is needed to verify this connection.

PREVENTION AND TREATMENT OF CANCERS ASSOCIATED WITH *P. GINGIVALIS* INFECTION

The prevention and treatment to those digestive cancers are specific and complicated for the existence of *P. gingivalis*. As a result, the intervention strategies are separate to antimicrobial therapy[72] and tumour site[73], but which both devote to thoroughly extracting carcinomas and managing good prognosis.

For that *P. gingivalis* owns the characteristics of high genetic capability, this bacterium could resist any adverse environment that hindering its development; *P. gingivalis* could also be capable of resisting various antibiotics that in use currently. In addition, the results of Deshpande *et al*[74]'s study indicated that *P. gingivalis* can actively invade endothelial cells with the help of fimbriae. Because of the specificity of this bacterium, the cancer treatment related to *P. gingivalis* is more directional and targeted. First, screening for *P. gingivalis* in dental plaques may identify susceptible subjects, which could help decrease the occurrence of cancers. Second, we can improve oral hygiene to reduce the risk of cancer. Third, the use of antibiotics or other antibacterial strategies may prevent the progression of cancers[36]. Blue light-emitting diode (BL) could inhibit the growth of *P. gingivalis* and play antimicrobial roles, and antimicrobial photodynamic therapy combining BL and rose bengal was expected to be a new technology for the elimination of bacteria[72]. Besides, AM404, an active metabolite of paracetamol, is an inhibitor of the growth and biofilm formation of *P. gingivalis* and could potentially make guidance in developing new drugs that is specific to infections and cancers with regard to *P. gingivalis*[75]. There are data suggesting that Kgp, a factor that playing the role of nutrition and toxicity for *P. gingivalis*, may act as the therapeutic point in controlling *P. gingivalis* infections. On account of it relating to the inhibition of other bacterial pathogens, protease inhibitors may have a potential to be an emerging antibacterial drug[76]. However, when cancers occur, treatment decisions are often complicated. The location, staging and resectability of the primary tumour, individual factors, such as swallowing function and airway condition, wishing to keep organ preserved, and coexisting diseases, all play roles in guiding accurate therapy. The main therapeutic approaches towards cancers are surgical therapy and radiotherapy[73]. During the last decade, the introduction of intensity modulated radiation therapy and concomitant che-moradiation have substantially changed the treatment techniques in head and neck cancer[77] and solved problems caused by radiotherapy, such as rapidly progressing dental caries as well as fungal and bacterial infections[78,79]. Recently, the chronological order between dental extractions and radiotherapy has also been fully demonstrated[80]. As for oesophageal cancer, the avoidance of radiotherapy is a valid choice. And the combination of platinum-based chemotherapy and radiotherapy before operation is the first choice in treating resectable local oesophageal carcinoma. In addition, the use of cisplatin and 5-FU combined with chemo-radiotherapy is an effective strategy for the treatment of ESCC. Surgical retention is a salvage procedure for patients with persistent or recurrent diseases. Several multicentre trials regarding neoadjuvant treatment for pancreatic cancer to improve survival are in progress[81]. With regard to pancreatic cancer, considering its characteristic of diagnosis in advanced stages, surgery tends not to be a selection; radiotherapy or chemotherapy is mainly used for palliative care[54]. Neoadjuvant therapy has become increasingly important in recent years, and further changes in standards are still needed[82]. The improvements in surgery, the advance of radiotherapy and the coordinated use of systemic drugs during treatment have clinically contributed to better outcomes of cancer patients[73]. In summary, the combination of antimicrobial therapy against *P. gingivalis* and tumour clearance with surgery, radiotherapy or chemotherapy, and

neoadjuvant therapy is a good treatment for these digestive system cancers caused by *P. gingivalis*. However, the prognosises of digestive cancers are not eventually same. As Woo *et al*[21] put, those OSCC patients who were infected with *P. gingivalis* are discovered more metastatic foci in the lung than those who were non-infected; ESCC patients those with high levels of IgA or IgG against *P. gingivalis* tend to worse prognosis and those who were detected with high both IgA and IgG were associated with worst prognosis[40]; Pancreatic cancer patients have suffered poor prognosis, partly for lacking diagnostic and prognostic biomarkers. It is better now for discovering the role of *P. gingivalis* in this devastating carcinoma, which would guide personalized treatments, improve prognosis and enhance the quality of life[43].

POSSIBLE MECHANISMS OF CANCERS CAUSED BY *P. GINGIVALIS*

Regarding cancer, diverse degrees of connections between *P. gingivalis* and tumours of the buccal cavity, digestive tract or pancreas have been displayed in multiple clinical and experimental studies[26,48,62]. The correlation of orodigestive cancer mortality to *P. gingivalis* was first and directly illustrated in a cohort study from Ahn *et al*[62], who pinpointed that *P. gingivalis* would also act as a microbial marker full of value in such carcinomas. In this study, non-parametric trend analysis for all subjects also showed an increase in orodigestive cancer mortality with the increase of anti-*P. gingivalis* IgG levels[62]. *P. gingivalis* interacts with host epithelium in varieties of aspects, which may provide basis at molecular level for potential mechanisms carcinogenesis mediated by this bacterium. In addition to *P. gingivalis* inducing the invasion of tumour cells and activating TLR mentioned above[30,31,33,50], other possible mechanisms have also been identified. First, nucleoside diphosphate kinase (NDK) excreted by *P. gingivalis* is capable of promoting tumourigenesis. The NDK inhibits ATP activation of purinergic receptor (P2X7) receptors and consequently depress the production of IL-1β in epithelium[83]. In that IL-1β plays a crucial role in priming IFNγ which could produce CD8+ T cells that specific to tumour antigen, and NDK secreted by *P. gingivalis* can also make tumour escape from immune surveillance[39]. The degradation of ATP mediated by NDK also suppresses apoptosis, which is dependent on ATP activation of P2X7 receptors[84]. Moreover, the phosphorylation of heat shock protein 27 (HSP27) by NDK from *P. gingivalis* confers an antiapoptotic phenotype to primary gingival epithelial cells, suggesting that HSP27 is a critical molecule for the suppression of host cell apoptosis caused by *P. gingivalis*[85]. Second, Yilmaz *et al*[84] have noted that the inhibition of epithelial cell apoptosis is an important carcinogenic effect of *P. gingivalis* and is also an intrinsic protective mechanism of cancerous cells. Activating the Jak1/Akt/Stat3 signalling, increasing the Bcl2 (anti-apoptosis): Bax (pro-apoptosis) ratio, curtailing releasing pro-apoptotic factor cytochrome c, and blocking activating both caspase-9 and the executioner caspase-3 may all contribute to this progression[38,86,87]. In addition, *P. gingivalis* modulates the expressing levels of microRNAs (miRNAs), and the upregulation of miR-203 caused by *P. gingivalis* results in the decreasing levels of negative regulator SOCS3 and subsequently suppressing apoptosis of epithelium[88]. Since SOCS3 can bind to phosphorylated JAK receptors, SOCS3 consequently inhibits JAK/STAT3 signalling[89]. Third, *P. gingivalis* infection induces expression of the B7-H1 receptor which belongs to the B7 family and plays a significant regulatory role in immunologic reaction mediated by cells[90,91], suggesting that this pathogen is involved in transferring to the distant and advancing nuclear grading of carcinoma cells[92]. On the other hand, B7-H1 receptors-mediated costimulatory signal could cause the anergy and apoptotic effect of those activated T cells, which subsequently make tumours evade immune reaction[93]. Fourth, those carcinogenesis caused by *P. gingivalis* also contributes to metabolising potential carcinogen. For instance, *P. gingivalis* could dehydrogenate ethanol to acetaldehyde which is a carcinogenic derivative and capable of making the damage of DNA, the mutation and excessive proliferation of the epithelial cells[24,25]. Certainly, the above contributions could suitably explain why excessive drinking is a risk factor for orodigestive cancer[39]. Lastly, *P. gingivalis* establishes chronic infections that involve intracellular persistence within epithelial cells[94]. Chronic inflammation has a close connection with the development of cancer for the release of inflammatory factors, such as IL-6, which can promote tumourigenesis by causing DNA hypomethylation as well as aberrant changes in promoter hypermethylation[95]. All the above-mentioned possible mechanisms of cancers caused by *P. gingivalis* are shown in Figure 1.
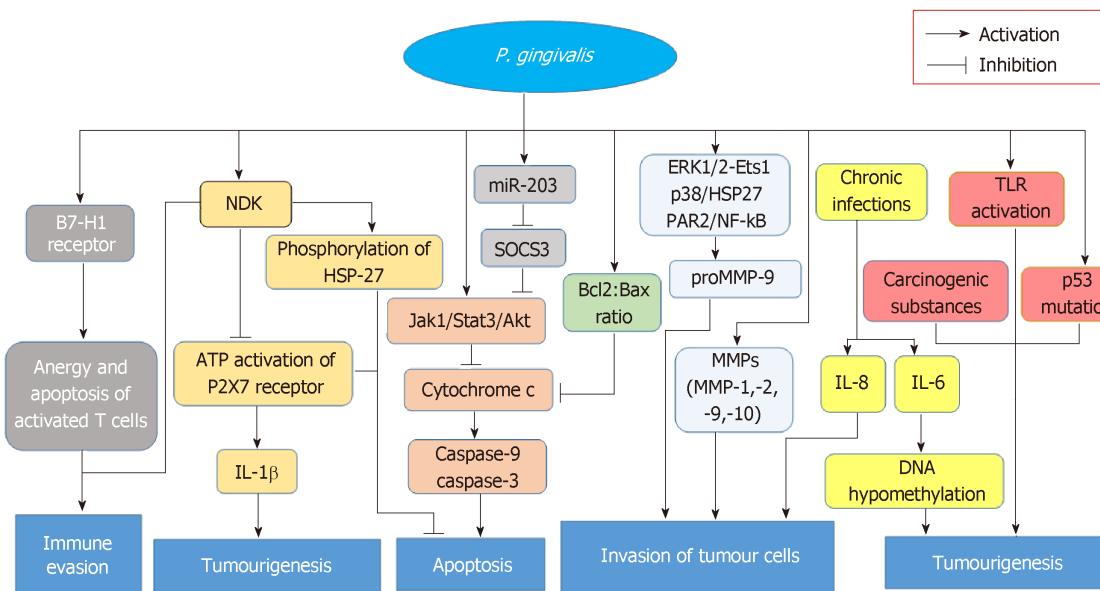
Figure 1 Possible mechanisms of cancers caused by *Porphyromonas gingivalis*. When *Porphyromonas gingivalis* (*P. gingivalis*) infects the host, the expression of the B7-H1 receptor is activated, contributing to anergy and apoptosis of activated T cells, which eventually leads to immune evasion. Nucleoside diphosphate kinas (NDK) from *P. gingivalis* antagonizes ATP activation of purinergic receptor (P2X7) receptors and thus reduces the production of interleukin-1β and promotes tumourigenesis. NDK also phosphorylates heat shock protein 27 (HSP27); the phosphorylation of HSP27 and ATP activation of P2X7 receptor both inhibit apoptosis. The upregulation of miRNA-203 leads to inhibition of the negative regulator suppressor of cytokine signaling-3 (SOCS3), and SOCS3 can play a role of inhibiting JAK/STAT3 signalling, while the activation of Jak1/Akt/Stat3 signalling pathways and the increased Bcl2: Bax ratio induced by *P. gingivalis* infection both curtail the release of cytochrome c and block the activation of caspase-9 and caspase-3 that positively correlate with apoptosis. By activating the ERK1/2-Ets1, p38/HSP27, and PAR2/NF-kB signalling pathways, *P. gingivalis* induces the expression of proMMP-9, and the levels of MMPs also substantially increase after *P. gingivalis* infection; both consequently promote the invasion of tumour cells. *P. gingivalis* causes the host to be in a chronic inflammatory state. Inflammatory factors, such as IL-6 and IL-8, are subsequently released; the former causes DNA hypomethylation and tumourigenesis, and the latter inhibits the levels of MMPs and makes connections with the invasion of tumour cells. Additionally, the metabolism of carcinogenic substances and the activation of TRL are involved in tumourigenesis as well. NDK: Nucleoside diphosphate kinase; P2X7: Purinergic receptor; IL-1β: Interleukin-1β; HSP27: Heat shock protein 27; miR-203: miRNA-203; SOCS3: Suppressor of cytokine signaling-3; Jak1: Janus kinase 1; Stat3: Signal transducer and activator of transcription-3; Akt: Protein kinase B; Jak1/Stat3/Akt: Jak1/Stat3/Akt pathway; ERK1/2: Extracellular signalregulated kinase 1 and 2; Ets1: Ever shorter telomere 1; PAR2: Protease-activated receptor 2; NF-kB: Nuclear factor-kappa B; proMMP-9: Pro-matrix metalloproteinase-9; MMPs: Matrix metalloproteinase; IL-8/IL-6: Interleukin 8/interleukin 6; TLR: Toll-like receptor; BCL-2: B cell CLL/lymphoma-2.

CONCLUSION

P. gingivalis is involved in periodontal disease and several cancers. This bacterium not only independently affects the development of cancers by RgpA, RgpB and Kgp[11,12] but also indirectly impacts cancers *via* periodontal disease that causes the host be in an inflammatory state[57,58]. One critical carcinogenesis caused by *P. gingivalis* is inhibiting the apoptotic effects of epithelium, which also function as the intrinsic protective mechanism of cancer cells[87]. *P. gingivalis* has a strong association with oral cancer, and the treatment of oral cancer is abundant and has been improved in the clinic. The significant function of *P. gingivalis* in oesophageal cancer was conducted by Gao *et al*[36] in 2017, which was considered a breakthrough in the research of oesophageal cancer and indicated that *P. gingivalis* can be an important biomarker for monitoring the occurrence and progression of this cancer. For pancreatic cancer, the evidence concerning the role of *P. gingivalis* is still limited, while the relationship between periodontal diseases and pancreatic cancer is very large[66-68]. Therefore, more investigations are still needed to reduce the incidence, increase the five-year survival rate and improve the treatments for this devastating cancer. Collectively, maintaining oral hygiene, seeking more biomarkers, improving therapeutic measures, and improving the prognosis of these diseases are the focus for clinical research and work in the future.

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