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Review

Carcinogenesis mechanisms of *Fusobacterium nucleatum*

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ABSTRACT

Transformed cells of cancers may be related to stromal cells, immune cells, and some bacteria such as *Fusobacterium nucleatum*. This review aimed to evaluate carcinogenesis mechanisms of *Fusobacterium* spp. in the oral cavity, pancreatic and colorectal cancers. These cancers are the three of the ten most prevalence cancer in the worldwide. Recent findings demonstrated that *F. nucleatum* could be considered as the risk factor for these cancers. The most important carcinogenesis mechanisms of *F. nucleatum* are chronic infection, interaction of cell surface molecules of these bacteria with immune system and stromal cells, immune evasion and immune suppression. However, there are some uncertainty carcinogenesis mechanisms about these bacteria, but this review evaluates almost all the known mechanisms. Well-characterized virulence factors of *F. nucleatum* such as FadA, Fap2, LPS and cell wall extracts may act as effector molecules in the shift of normal epithelial cells to tumor cells. These molecules may provide new targets, drugs, and strategies for therapeutic intervention.

Contents

1. Introduction

Malignant cancers are complex communities of oncogenic potentially transformed cells with inappropriate genomes. Transformed cells are associated with non-neoplastic cells including stromal and immune cells, and sometimes microbes, including bacteria and viruses [1]. Some bacteria, such as *Fusobacterium nucleatum*, *Prevotella gingivalis*, *Prevotella melaninogenica*, *Helicobacter pylori*, *Salmonella typhi*, *Streptococcus bovis*, *Streptococcus mitis*, *Chlamydia pneumoniae*, and *Capnocytophaga gingivalis* may cause different types of cancers in human [2–6]. *P. gingivalis*, *P. melaninogenica*, *S. mitis*, *Escherichia coli* and *F. nucleatum* can cause oral squamous cell carcinoma (OSCC) [2,7–9]. *F. nucleatum* has an increased risk of colorectal cancer and pancreatic cancer [10–12]. *H. pylori* is the most common organism associated with gastric cancer or mucosa associated lymphoid tissue (MALT) lymphoma and can reduce the risk of esophageal cancer [3,4]. *S. typhi* has been associated with the gallbladder and is an engaged carrier of therapeutic agents for colon, gallbladder cancer and melanoma [5,6]. *S. bovis* has been associated with colon and colorectal cancer [13,14] and *C. pneumoniae* is associated with lung cancer [15,16]. *E.*

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coli serotypes such as enterohaemorrhagic *E. coli* (EHEC) and enteropathogenic *E. coli* (EPEC) have increased risk of colorectal cancer (CRC) by adherence to embryonic intestinal cells and colon adenocarcinoma cells and release toxins such as CNF, CDT and CIF [8,17]. The cytolethal distending toxin (CDT), cytotoxic necrotizing factor (CNF) and cycle inhibitory factor (CIF) are *E. coli* cyclomudlins that interfere with eukaryotic cell cycle [17]. CDT and Cif inhibit clonal expansion of lymphocytes. CNF interferes with cell differentiation and development pathways [17]. Also, it has been estimated that at least six human viruses contribute to 10–15% of the cancers worldwide, such as Epstein-Barr virus (EBV), human papilloma virus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), Kaposi's associated sarcoma virus (KSHV) and human T-cell lymphotropic virus (HTLV-1) [18]. Important mechanism that can induce carcinogenesis include: chronic infection or toxins production, immune evasion and immune suppression [19]. Chronic infection may cause to disturb the cell cycle and resulting in modified cell growth, also in addition, toxin production can cause damage to DNA by carcinogenic agents and followed by damage to genes and modified control normal cell division and apoptosis [20]. Bacterial strategies of toxic warfare a cell cycle control are: (I) the cell cycle inhibitors, such as the cycle inhibiting factor (Cif), cytolethal distending toxins (CDT), and block mitosis, (II) compromise the immune system by inhibiting clonal expansion of lymphoma, (III) the cell cycle stimulators, such as cytotoxic necrotizing factor (CNF) [17]. *Fusobacterium* spp. are a group of anaerobic, non-spore forming, fusiform or spindle shaped rods, non-motile and gram negative bacteria [21]. *F. nucleatum* is an anaerobic, pro-inflammatory, invasive and adherent bacterium [22]. *Fusobacterium* spp. can colonize the oral cavity, but can inhibit the gut [21]. *F. nucleatum* are frequently involved in head and neck disease, gut disease, such as inflammatory bowel disease (IBD), ulcerative colitis (UC), Crohn's disease, respiratory tract infections, such as chronic otitis, sinusitis, peritonsillar abscesses, cerebral

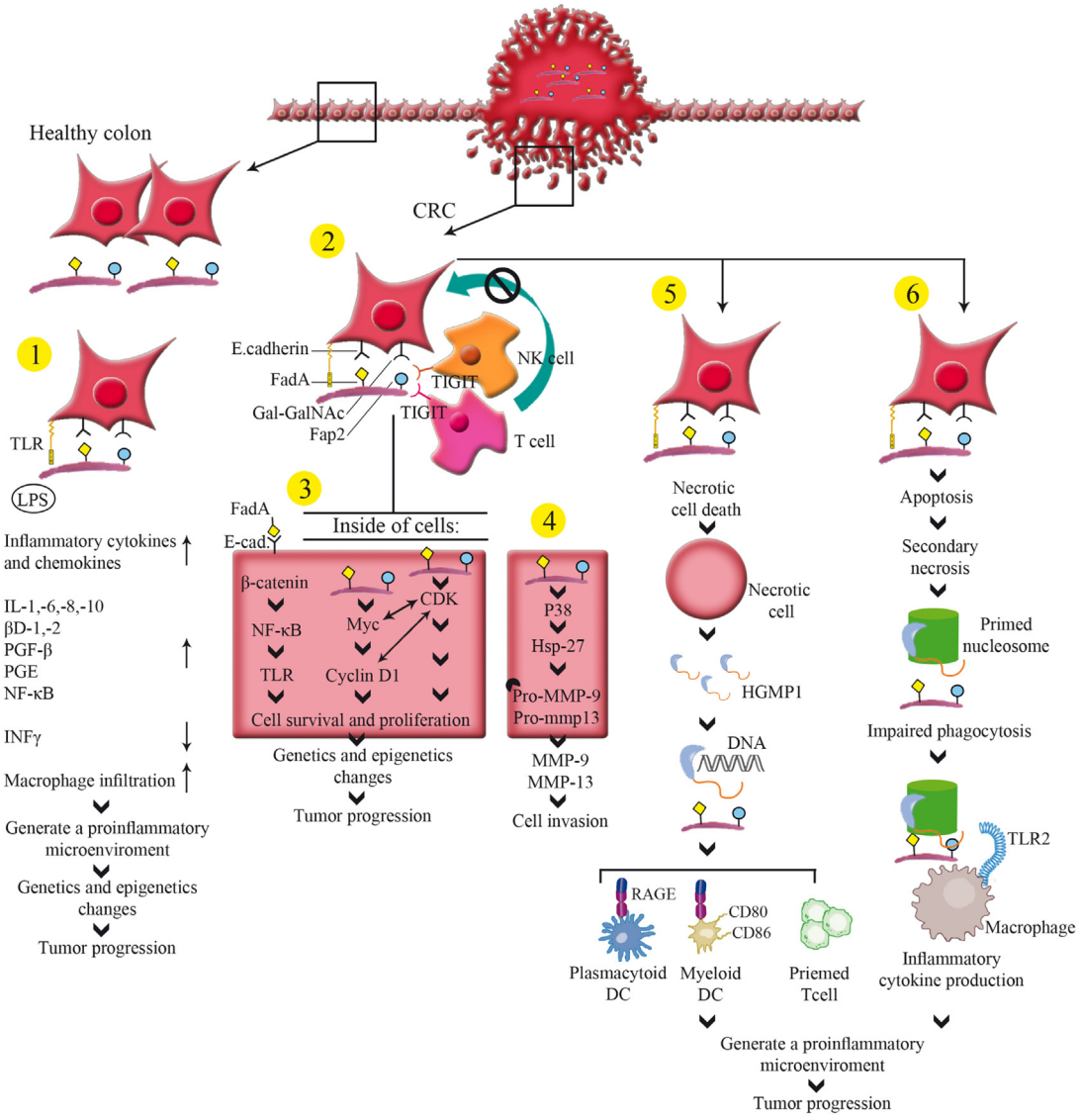

Fig. 1. A model for the role of *F. nucleatum* in oral and colon cavity cancer. In pathway 1, LPS and cell extracts of *F. nucleatum* by impact on CRC increase inflammatory cytokines and chemokine and generates a proinflammatory microenvironment that promotes tumor progression. In pathway 2, the Fap2 protein of *F. nucleatum* interacts with the TIGIT receptor of immune cells, resulting in the inhibition of NK and T cell activities and generate a proinflammatory microenvironment. Gal-GalNAc receptor binding to Fap2 may reduce *F. nucleatum* potentiation of CRC. In pathway 3, FadA binding to E-cadherin activates β-catenin signaling, leads to increase of proinflammatory cytokines, Wnt signaling, oncogenes, such as Myc and cyclin D1, and stimulation of cell proliferation. In pathway 4, activation of P38 leads to secretion of MMP-9 and MMP-13, which causes cell invasion. In pathway 5 and 6, cell inflammation by *F. nucleatum* results in necrotic and apoptotic cells. The interaction between the product of necrotic, apoptotic cells and HMGB1 generate a proinflammatory microenvironment that cause tumor progression.

abscesses, hepatic abscess and pancreatic abscess, lung abscesses, aspiration pneumonia, pericarditis, one of the species responsible for lemierre's syndrome and can induce bacteriemia and intracranial infections [23–29]. Many studies have demonstrated the importance and synergistic potentials of *Fusobacterium* spp. relative to other organisms in mixed infections [24]. Oral cancer, colorectal cancer and pancreatic cancer are the three of the ten most prevalence cancer in the worldwide [30–33]. According to the national cancer institute data in the united states during the year 2016, approximately, 48,330 new cases and 9570 deaths were estimated for oral cavity and pharynx cancer, 53,070 new cases and 41,780 deaths for pancreatic cancer and 95,270 new cases and 49,190 deaths from colorectal cancer [32]. In addition, recent findings based on bacterial 16s ribosomal RNA (16srRNA) gene DNA sequencing, transcriptome sequencing or metagenomic analysis using whole genome sequencing has investigated the importance and potentials of *Fusobacterium* spp. in oral cancer, pancreatic cancer, colorectal cancer, and colitis associated colorectal cancers [11,12]. Based on these findings, we were reviewed roles of *Fusobacterium nucleatum* in oral, pancreatic and colorectal cancer papers and relevance of the abstracts and full texts on papers were studied tumorgenesis mechanisms of *F. nucleatum* in these cancers in 20 years back and up to end of November 2016 (Fig. 1).

2. Colorectal cancer

Several researches associated with *Fusobacterium* spp. and colon cancer showed that direct or indirect role of *Fusobacterium* spp. in colon cancer remains unclear but some studies demonstrated that abundance of *Fusobacterium* spp. in gut tissue associated with some disorders and suggested that *Fusobacterium* spp. may be cause the colorectal carcinoma [12,23,34–37]. Findings of these researches are summarized in enrichment of *Fusobacterium* spp. in patients with adenomas and colorectal carcinomas, contributing to tumorgenesis by affecting and expanding of immune cells. *Fusobacterium*-associated human colorectal cancer genes are including *fadA* with interaction with endothelial cells and epithelial cells and interaction between *F. nucleatum* Fap-2 and Gal-GalNAc [38]. In a novel study, such as Abed et al. demonstrated that *F. nucleatum* Fap-2 binds to Gal-GalNAc as a polysaccharide receptor of CRC [38]. In their study, intravenously injection of *F. nucleatum* in mice suggested that fusobacteria use a hematogenous route to arrive colon carcinoma [38]. These findings suggested that targeting host Gal-GlaNAc receptor or Fap-2 may reduce *F. nucleatum* potentiation of CRC [38]. Gur et al. demonstrated that *F. nucleatum* Fap2 protein engages TIGIT on NK and T cells followed by interfering with the host immunity attack to Fusobacteria tumors [39]. Fap2 may protect *Fusobacterium* tumors from host immunity attack. TIGIT is an inhibitory immune receptor on NK and T cells [40]. Unlike the other bacteria associated to colorectal adenoma, *F. nucleatum* does not intensify enteritis, colitis or inflammation-related intestinal carcinogenesis. Totally, *Fusobacterium* spp. recruits tumor-infiltrating immune cells, follow as, generates a proinflammatory microenvironment that able to transmit to colorectal carcinoma progression [12]. Garrett et al. and Uronis et al. studies have shown that absence of the gut microbiota or antibiotic treatment decreased tumor incidence in most of the murine colitis associated CRC models [35,37]. Several recent studies such as McCoy et al., Sanapareddy et al., and etc. have performed case-control researches of colorectal cancer using 16srRNA gene surveys, with one attending fusobacterial enrichments in their patients [11,41]. Also, Kostic et al. studies have measured *Fusobacterium* spp. presence in pairs adenoma tissue and normal tissue from the same patient, and have found that *Fusobacterium* spp. were presented in 48% of adenoma patients and those cases that were positive. These organisms were enriched in adenoma compared to surrounding tissues [12]. Kostic et al. have found that *Fusobacterium* spp. presence were a higher overall presence in the fecal microbial of CRC patients compared to healthy control people [12]. These findings suggested that *F. nucleatum* begins to accumulate at the primary stages of colonic tumorgenesis in some groups of patients. Also, Kostic et al., study has shown that *F. nucleatum* count had higher in small intestinal aberrant cryptic foci (ACF), adenocarcinoma and adenoma as compared to other microbial such as *Streptococcus* spp. as control [12]. As well as, Castellarin et al. study confirmed these results that *F. nucleatum* associated with lymph node metastasis in gut tissue and abundance of *F. nucleatum* was highly significant in colorectal tumor specimens compared with control [34]. Also, they suggested that *F. nucleatum* presence may be used as colorectal cancer and CRC risk biomarker [34]. These studies showed that *F.nucleatum* could accelerate in the presence of macroscopic inflammation or enteritis. Collectively, presence of *F. nucleatum* in intestinal effects on immune cells, especially myeloid-derived immune cells and their effectors, which are key components of the tumors and promote neoplastic progression. *Fusobacterium* tumor increase $CD11b^+$ myeloid cells, myeloid-derived suppressor cells (MDSCs), and tumor-associated neutrophils (TANs), tumor-associated macrophages (TAMs), M2-like TAMs, classical myeloid DCs, $CD103^+$ regulatory DCs [12,42]. But numbers of $CD3^+$ $CD8^+$ and $CD3^+$ $CD4^+$ T cells were not significantly different [12,42]. While Th17 cells and $FoxP3^+$ regulatory T cells (Treg) in *F. nucleatum* tumor have been increased significant heterogeneity did not correlate with intratumoral *Fusobacterium* abundance [12,42,43]. $CD11b^+$ myeloid cells members are granulocytes, macrophages and dendritic cells (DCs). These cells play a major role in angiogenesis and promoting tumor progression [44,45]. The strategies of $CD11b^+$ myeloid cells against tumor cells are T cell suppressive activity, inducible nitric oxide synthase (iNOS) and arginase-1 expression [44,45]. Two principal MDSC subsets are granulocytic (G-MDSC) and monocytic (M-MDSC). These cells are tumor-permissive cells with potent immune suppressive activity [46,47]. Both of G- and M-MDSC increased in *F. nucleatum* tumors [12,42]. Arginase activity, is found in the tumor microenvironment and serum of patients with prostate cancer [48] breast [49], skin [50], and colorectal carcinoma [51]. Some studies showed that arginase have been expressed or released by either tumor-associated myeloid cells, including putative MSCs or cancer cells [52–54]. Two different forms of arginase are arginase-1 (liver arginase) and arginase-2 (kidney arginase). Arginase-1 is inducible and cytoplasmatic, but arginase-2 is constitutively and mitochondrial expressed [55]. Both of them convert L-arginine into L-ornithine, as an essential compound for the generation of polyamines. Arginase directly promotes tumor progression, and molecules crucial for both tumor proliferation and cell transformation [56]. Arginase activity has been proposed as a marker of tumor progression in patients with intestinal adenocarcinoma [57], colon-rectal carcinoma [51] and breast cancer [58]. Serafiny et al. and Bronte et al. have showed the importance of arginase expressing myeloid suppressor cells (MSCs) on possible deletion and inhibition of tumor-specific CTL [52,59]. In particular, Rodriguez et al. study showed that arginase-1 induced by IL-13 and IL-4 [53]. Arginase-1 can down-regulate the expression of the ζ-chain of T-cell co-receptor molecule CD3 [53]. MSC arginase can increase super-oxide production in myeloid cells through a pathway, which presumably utilizes the reductase domain of iNOS [52,60]. iNOS is likely that super-oxide [3] and its byproducts, such as hydrogen peroxide or peroxynitrites [61], are required for arginase-1-dependent suppression of T cell functions since the combination of iNOS and arginase-1 inhibitors, an iNOS reductase domain inhibitor [52], peroxynitrite scavengers [3] or catalase [61], can all revert the MSC suppressive phenotype. iNOS plays a role at least in two mechanisms of suppressive pathways in

myeloid suppressive cell [54]. In the first mechanism, iNOS require the synergistic interaction with the production of super-oxide, NO and arginase-1 by iNOS [53]. The second mechanism of iNOS likely depends entirely on iNOS. Myeloid suppressive cells by expressing only iNOS, may be inhibited peptide-specific responses and mitogenic through NO production. Myeloid suppressive cell-mediated T cell inhibition is not associated with an inability to up-regulate the early activation markers CD25 and CD69 or a loss in IL-2 production, but results in the direct impairment of the main signaling pathways coupled to the IL-2 receptor as demonstrated by the lack of extracellular signal-regulated kinase, STAT5, JAK3, and Akt phosphorylation in response to IL-2 [62]. Also, *F. nucleatum* induced myeloid derived cell expansion in intestinal tumors [12]. Kostic et al. showed a correlation of immune cell marker genes associated with DC (*CD11c/ITGAX, CD209, CD80* and *TNF*), MDSC (*CD33* and *IL6*) and TAM (*CD209, CD206/MRC1, CXCL-10, IL6* and *IL8*) with *Fusobacterium* frequency in human *Fusobacterium*-associated tumor [12]. Also, a few studies showed that many of the top ranked *Fusobacterium* associated genes *TNF-α, IL1β, IL6, IL8* and *PTGS2 (COX-2), NF-κB and MMP3* have not only investigated in carcinogenesis, but also are induced by *Fusobacterium* spp. in coculture with mouse and human cell lines in vitro [12,63,64]. *TNF-α, IL1β, IL6, IL8* and *PTGS2 (COX-2),* and *MMP3* was suggestive of an NF-κB-proinflammatory response as a central link between inflammation and cancer that increased in *Fusobacterium* spp. abundance in human CRCs [12,65]. Immunobloting analyses and RNA sequencing studies suggested a strong association between specific immune pathways and genes and *Fusobacterium* spp. abundance [12]. Kostic et al. studies showed that *Fusobacterium*-associated proinflammatory genes identified in human tumors, such as *IL6*, *Tnf* (*TNFα*), *Mmp3Ptgs2*, and *Scyb1*, were highly expressed in both colon tumors and small intestinal and were higher in the colonic tumors compared to intestinal tumors [12], and this may be related to intrinsic to the anatomical site. FadA is a virulence factor of *Fusobacterium nucleatum* that expressed on the bacterial surface [66]. Several studies suggested that FadA adherences to, invades to, and induces inflammatory and oncogenic responses to stimulate growth colorectal carcinoma cancer cells through FadA adhesion [66,67]. FadA exists in the non-secreted interacted pre-FadA form and the secreted mature FadA (mFadA) form that consisting without 18 amino acids signal sequence. Active complex of FadA is FadAc, when formed mFadA is mixed with pre-FadA. FadAc consist of heterogeneous filaments. FadAC presumably due to varying to degrees of filament bundling [68,69]. The receptor of FadA on the endothelial cells is the vascular endothelial cadherin (CDH5) that is a member of the calcium-dependent adhesion glycoproteins (cadherin super family) that binds to β-catenin [70,71]. CDH5 is required for *F. nucleatum* to attach and invade endothelial cells [71]. Another receptor of FadA is E-cadherin on non-CRC and CRC cells. FadA binding to E-cadherin mediate *F. nucleatum* attachment of epithelial cells and invasion into these cells. Following that, activates β-catenin signaling that leading to increased expression of inflammatory genes, transcriptional factors, *wnt* genes and oncogenes [72]. FadAc binds specially to E-cadherin-5 (EC5). EC5 is the transmembrane or the cytoplasmic domains of E-cadherin [70]. FadAc, but not mFadA, binding to EC5 leads to E-cadherin phosphorylation on the membrane and FadAc-EC internalization. FadAc-EC decrease β-catenin phosphorylation in the cytoplasm and translocate it into nuclease that cause by activation of β-catenin-regulated transcription (CRT). CRT activates and increases the expression of transcription factors such as lymphoid enhancer factor (LEF-1), T cell factor (TCF1, TCF3, TCF4), *wnt* signaling genes, including *wnt7a*, *wnt7b*, *wnt9a*, oncogenes cyclin D1 and *myc*, protein tyrosine kinase such as *ptk6*, clathrin such as *cltb*, NF-κB such as NF-κB2 and proinflammatory cytokines such as IL-6, IL-8 and IL-18 [73,74]. LEF/TCF complex plays an important role in the development of colorectal carcinoma. Wnt signaling pathway activation is a cause of colon cancer. Wnt signaling activation caused by genetic mutations which stabilize the β-catenin protein and permitting it to gather in the nucleus and form complexes with LEF1 and any of TCF1, TCF2, TCF4 [75,76] to activate *myc*, CCND1, MMP7 and TCF7 as target genes in colon cancer.

3. Oral cancer

More than 700 species of bacteria, including 11 bacteria phyla and 70 genera inhibit the oral cavity [77]. The oral cavity environment is influenced by systemic and local factors [9,78]. Systemic factors are included into irregular lifestyle, consumption of alcohol, smoking, obesity, eating habits, heredity, hormones, and stress [9,78]. Local factors are included into tartar, teeth alignment, dental plaque, an incompatible prosthesis, occlusion and bad life style [9,78]. Epidemic studies suggested that the risk of the oral cavity cancer is increased in people that tooth loss or periodontal disease and disorder caused by oral bacteria [79,80]. Oral disease such as periodontitis have been associated with the risk of the oral cavity and gastrointestinal cancers such as tongue, esophagus, colon and pancreatic cancers [10,31,39,81]. According to national cancer institute data, oral cavity cancer is included to tongue, mouth, pharynx and other oral cavity cancer [32]. Several recent studies demonstrated that periodontitis is associated with tongue cancer, oropharyngeal squamous cell carcinoma (SCC), laryngeal SCC, oral cavity SCC and other head and neck cancer. Totally, oral cancer caused by bacteria associated with colonization of epithelial cell, periodontitis, ability to carcinogenesis producing cursors, metabolize precarcinogenesis components, direct toxic effects of bacteria, indirect effects of inflammation and their products and modification in the microenvironment [9,82–88]. Because of abundance *F. nucleatum* and its ability to congregate with other species in the oral cavity, this bacteria is a key organism of periodontal plaque. Elevated *F. nucleatum* levels were detected significantly in people with oral SCC compared with that in people with normal oral squamous cells [89,90]. Some researches demonstrated that periodontitis is associated with CVD (cardiovascular disease), endothelial dysfunction and atherosclerosis [88]. Findings of Han et al. showed that pathogens that caused periodontitis is induced anticardiolipin-1 (anti-c1) by molecular mimicry of B2-glycopritein I [88]. Anticardiolipin is a group of autoantibody termed "antiphospholipids" antibody [88]. Anticardiolipin is associated with CVD and adverse pregnancy [88]. Frequent *F. nucleatum* infection in gingival is associated with bleeding translocation of these bacteria during gestation from mother's oral cavity to the uterus when the immune system was weakened in relation to infectious disease [91]. This translocation is associated with pregnancy complications such stillbirth, preterm birth and early onset neonatal sepsis [91–93]. Epithelial cells of oral cavity are known as squamous cell. OSCC or oral squamous cell carcinoma is a malignancy that may appear in any location of oral cavity [94,95]. The locations of this malignancy are tongue, back of the tongue, buccal mucosa, retromolar area, gingiva, floor of the mouth, soft palate, hard palate and lip. Because the rate of OSCC is more than 90% of all oral cavity cancers [94,95], we are focused on the role of *F. nucleatum* on OSCC.

Pushalkar et al. results illustrated that *F. nucleatum* subspecies *vincentii* was detected at squamous cell carcinoma site while *F. nucleatum* subspecies *nucleatum* was detected at the non-tumor site [90]. But Hooper et al. illustrated that *F. naviforme* and *F. nucleatum* subspecies *nucleatum* were detected at deep and

overlaying of tumor [89,96]. Recent studies demonstrated that expression of cytokines such as IL-1, IL-10, TNF and chemokine such as CCL2 are high expressed in cancer associated inflammation [97,98]. Abiko et al. findings showed that β-defensin-1 (BD-1) and β-defensin-2 (BD-2) expression in squamous cell carcinoma is up regulated by stimulation with TNF-α and LPS [99]. LPS of *F. nucleatum* results in inflammatory and cytokine-mediated damaging lesions of the gingiva [100]. BD-1 and BD-2 are antibacterial and antifungal peptides that produced by epithelial cells of the salivary gland, pancreas, kidney, trachea and oral epithelium. Abiko and Krisanaprakornkit studies suggested that reducing in expression of BD-1 and -2 in squamous cells may be susceptible to infection [99,101]. Krisanaprakornkit et al. demonstrated that BD-2 induced by lipopolysaccharides extracted from the cell wall of *F. nucleatum* and tumor necrosis factor alpha (TNF-α) [101]. TNF-α is an intermediary in *F. nucleatum* signaling [101]. also LPS of *F. nucleatum* up regulated the expression of IL-8 [101]. Ji et al. demonstrated that *F. nucleatum* infection induced the expression of BD-2 and BD-3 by gingival squamous cells [102]. Also demonstrated that NALP2 (NACHT-LRR and pyrin domain – containing protein 2) and TLR-2 reduced the induction of BD-3 but not induction of BD-2 and IL-8 [103]. *F. nucleatum* is able to activate JNK and TLR-2 signaling pathways. The promoter region of BD-2 includes different types of regulatory elements, such as AP-1, AP-2, NF-IL-6 and NF-κB binding sites, while BD-3 promoter includes no apparent NF-κB binding sites [104]. Infection by *F. nucleatum* in gingival epithelial cells activates NLRP3 inflammasome [105]. NLRP3 inflammasome activation activates caspase-1 and induces secretion of mature IL-1β [105]. Also, *F. nucleatum* infection activates induction of translocation of NF-κB into nucleus and follow that cytokine gene expressed [105]. *F. nucleatum* infection can induce other DAMPs (damage-associated molecular patterns) that mediate inflammsome including HMGB1 (high-morbility group box-1 protein), apoptosis-associated speck-like protein (ASP) with a similar time-coarse as caspase-1 activation [105]. HMGB1 is a nuclear protein that binds to DNA [106,107]. In addition, HMGB1 associates with cytokines and TLR ligands [106,107]. HMGB1 can activate cells through RAGE, TLR2 and TLR4 [106,107]. RAGE (receptor for advanced glycation end products) is a multi-ligand receptor that binds to AGE (advanced glycation end products) [108], β sheet fibrils, such as amyloid β [109], S100 family proteins such as S100A8/9 [110], RNA, DNA and HMGB1 [111]. RAGE activation has been implicated in diabetes [112], Alzheimer's disease [113], inflammation and cancer [111,114]. Several studies demonstrated that over expression of HMGB1 occurs in colon cancer, melanoma, breast cancer, pancreatic cancer and prostate cancer [114,115] and may related to invasion and metastasis [115,116]. Tumor cell metastasis by HMGB1 may be directed involved through its ability to modulate the adhesive properties of cells, to promote cell migration and to modify the components of extracellular matrix [117,118]. RAGE signaling pathways include the activation of MAPKs [119], NF-κB [119,120], PI3K/Akt [121], JAK/STAT [122], Rho GTPases [123] and Src family kinase [124]. Singh et al. suggested that activation of PI3K\Akt pathway occurs in squamous cell carcinoma [121]. NF-κB signaling cause TLR activation [125]. Totally, interaction between HMGB1 and RAGE may cause to oral inflammation and oral cancer. However, more studies that are detailed are needed to be done on *F. nucleatum* carcinogenesis by HMGB1-RAGE signaling.

F. nucleatum activates *p38* followed by heat shock protein-27 (HSP-27) and secretion of matrix metalloproteinase-9 and MMP-13 [7,9,126,127]. Cell wall extracts of *F. nucleatum* induce human beta defensins like HβD2 and HβD3 and inflammatory cytokines like IL1α, IL1β, IL6, IL8 and MMPs [128]. MMP-9 and MMP-13 cause invasion and metastasis phenotype. Kao et al. and Patel et al. suggested that MMP-9 and MMP-13 may be useful for treatment monitoring and detection of metastatic phenotypes in oral cancer [127,129].

4. Pancreatic cancer

Few studies have examined the role of *Fusobacterium* spp. in pancreatic disorders and cancer. Lown et al. has shown that *Fusobacterium* spp. play a role in the development of pancreatic cancer probability [10]. *Fusobacterium* spp. has presented in 8.8% of pancreatic cancer and the presence of these bacteria may be associated with the malignant potentials. Bacteria getting from the pancreatic tissues by dissemination has documented in human subjects. Bacterial translocation from the oral and intestinal tract leads the presence of *Fusobacterium* spp. within the pancreas. Also, *Fusobacterium* spp. is associated with some inflammatory and disorders, such as hepatic abscess [25,29] and pancreatic abscess [28,130]. Furthermore, several studies have demonstrated that the oral microbiome overlaps with the other organs microbial such as intestinal microbiota and cause to different cancers, such as gastric cancer, colorectal cancer and etc. [7,9,131,132]. Further studies are needed to determine the role of *Fusobacterium* spp. in the development of pancreatic cancer.

5. Conclusion

Fusobacterium nucleatum could be causative agent of malignancy cancers such as colorectal cancer, pancreatic cancer and oral squamous cell cancer. There are some uncertainty carcinogenesis mechanisms about these bacteria, but we tried to review almost all the known mechanisms. Improved oral hygiene, personal health, use of probiotic food, quickly and effectively treated of infection could prevent colorectal cancer, pancreatic cancer and oral cancer. Finally, well-characterized virulence factors of *F. nucleatum* such as FadA, Fap2, LPS and cell wall extracts may act effector molecules in the shift of normal epithelial cells to tumor cells. These molecules may provide novel drugs, targets and strategies for therapeutic intervention.

Conflict of interest

Non to declare.

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