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Role of bacterial infection in the development and progression of gastric cancers

Abstract

Bacterial infection can be associated with the development of cancers, especially in organs that are constantly exposed to bacteria, such as gastrointestinal tract. The epithelial cells represent the first barrier for bacteria invading the body and are participated in inflammatory responses and innate immune responses. Epithelial cells and non-epithelial cells exposed to bacteria release diverse proinflammatory mediators to activate and attract immune cells to the site of infection. Bacteria-induced inflammatory mediators and cytokines may promote carcinogenesis in inflamed tissue or increase neoangiogenesis, and tumor cell proliferation, survival, and migration in the tumor microenvironment. In this review, bacteria-induced inflammation and carcinogenesis, association of Helicobacter pylori infection with gastric cancer, as well as molecular mechanisms involved in Helicobacter pylori-promoted gastric inflammation and carcinogenesis are discussed.

Keywords: bacterial infection, inflammation, immune responses, carcinogenesis, Helicobacter pylori, gastric cancer, proinflammatory, neoangiogenesis, proto-oncogenes, immunodeficiency, lymphotropic virus, peroxynitrite, granulocyte-monocyte, retinoblastoma, astrocytoma, squamous

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Introduction

At present, cancer is the second leading cause of death worldwide, accounting for an estimated 9.6 million deaths in 2018.[1] This type of diseases elicits from uncontrolled growth and proliferation of malignant cells harboring genetic alterations. These abnormally growing and proliferating cells can have a life-threatening effect when they physically or pathologically affect adjacent healthy cells in a vital organ. Distinct genetic alterations within a cell that result in out of control cell proliferation are responsible for the initiation of cancer formation. In this regard, genetic alterations in proto-oncogenes and tumor suppressor genes are frequently reported in several cancer cell types. Prolonged exposure to various mutagens can be involved in the induction of these genetic alterations in cancerous cells.[2] Chronic infection represents a risk factor for cancer development. It has been estimated that up to 20% of the global cancer burden is attributed to infectious agents, especially viruses and bacteria.[3,4] The bacterium Helicobacter pylori and viruses Hepatitis B virus, Hepatitis C virus, certain strains of human papillomavirus, Epstein-Barr virus, human immunodeficiency virus type-1, and human T-cell lymphotropic virus type-1 have been identified as major carcinogenic infectious agents by International Agency for Research on Cancer (IARC).[3] These infectious agents are highly prevalent in the world. Nevertheless, most infected individuals do not develop cancer, indicating that genetic susceptibility of host and environmental factors may be associated with cancer caused by these infectious agents. Gastrointestinal tract is constantly exposed to many bacterial agents and some of these agents induce chronic inflammation in this organ. On the other hand, chronic inflammation may increase the rate of mutation in epithelial cells leading to cancerous cell formation. As discussed below for gastric cancer, some evidences suggest that specific bacteria can be involved in cancer development or progression. These bacteria can trigger oxidative stress in host cells, activate some intracellular pathways such as nuclear factor-kappa B (NF-κB) pathway, and promote production of various components involved in carcinogenesis. Role of inflammation in induction of oxidative stress and NF-κB pathway activation and cancer development, Phagocytosis of bacteria initiates oxidative stress in the phagocytic cells leading to release of reactive oxygen and nitrogen species such as peroxynitrite, reactive hydroxyl group, and other free radicals. These reactive components produced by inflammatory cells at site of infection affect enzymatic activities and expression of several genes. They can also induce DNA damage and genomic instability. Indeed, nucleotide modifications induced during oxidative stress can lead to mutagenesis. Some critical mutations and genomic instability, if not properly repaired, have the potential to orchestrate events in precancerous cells resulting in resistance to stress and death signals, and induce aberrant cell proliferation. Oxidative stress is linked to NF-κB pathway activation.[4,5] Activation of NF-κB is involved in the immediate-early innate immune responses in microbial infections.[6] NF-κB exists in the cytoplasm of many different cells and is bound to IkappaB (IκB), which prevents it from entering the nucleus. When cell is stimulated, NF-κB is released from IκB, enters into the nucleus and binds to specific sequences in promoter regions of target genes and upregulates their transcription. Activated NF-κB regulates transcription of several genes encoding growth factors, cytokines, chemokines, cell adhesion molecules, proinflammatory enzymes, angiogenesis factors, and apoptosis-related proteins. Accordingly, NF-κB has important roles in various cell functions such as in cell proliferation by activating growth factors such as IL-2, granulocyte-monocyte colony stimulating factor and CD40L,[7,8] in cell cycle progression by activating c-myc and cyclin D1,[7,9] and in inhibition of apoptosis through regulation of the anti-apoptotic proteins ciAPS, c-FLP and members of the Bcl-2 family.[7–11] Activation of NF-κB also leads to upregulation of vascular endothelial growth factor (VEGF) and matrix metalloproteinase (MMP) that are associated with angiogenesis and cell migration, respectively. Furthermore, NF-κB is involved in overexpression of cyclooxygenase-2 (COX-2), an enzyme regulating prostaglandin synthesis,[12] which has a role in cell proliferation,[13–15] migration,15 invasion,15 apoptosis, and angiogenesis.[14–18] COX-2 also contributes to immune evasion.[19] The

NF-κB pathway is participated in the regulation of immune responses during inflammation as well as in carcinogenesis. Activation of NF-κB pathway and its cooperation with multiple other signaling pathways and molecules occurs in chronic inflammation and triggers transcription of several proinflammatory cytokines genes, cell cycle-related genes, and downregulation of apoptosis-related genes.[20] Aberrant NF-κB signaling has been identified in various types of cancer, including esophageal cancer, gastric cancer, colon cancer, breast cancer, lung cancer, hepatocellular cancer, pancreatic cancer, melanoma cancer, endometrial cancer, ovarian cancer, bladder cancer, prostate cancer, thyroid cancer, parathyroid cancer, laryngeal cancer, retinoblastoma, astrocytoma, squamous cell carcinoma of the head and neck, and hematopoietic malignancies, such as multiple myeloma, chronic lymphocytic leukemia, adult T cell leukemia, acute myeloid leukemia, chronic myeloid leukemia, Hodgkin's lymphoma, mantle cell lymphoma, MALT lymphoma, diffuse large B cell lymphoma, and myelodysplastic syndrome.[21–23] Constitutive activation of NF-κB in different types of cancer suggests its possible involvement in mechanisms connecting inflammation and cancer development, as this pathway is related to inhibition of apoptosis, promotion of cell survival and proliferation, and tumor invasion and metastasis. Inflammation-induced and NF-κB-mediated downstream pathways and molecules involved in carcinogenesis.

Cytokines released during inflammation may contribute to cancer development. Various stimuli such as proinflammatory cytokines tumor necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β), as well as Toll-like receptor (TLR) ligands activate NF-κB pathway.[24] This NF-κB pathway, known as the classical or canonical pathway of NF-κB, is essential for innate immunity and inhibition of apoptosis under conditions of infections.[25–27] NF-κB is also activated by an alternative pathway through TNF receptor superfamily members such as lymphotoxin β (LT), CD40 ligand, BAFF, and receptor-activated NF-κB ligand (RANKL). NF-κB alternative pathway regulates cell survival and is critical for development and function of secondary lymphoid organs. NF-κB-induced upregulation of antiapoptotic gene Bcl-xL expression was detected in human T cells[28] and human hepatocellular carcinoma cells.[29] In addition, overexpression of cyclinD1, a cell cycle regulator required for G1 phase progression which is induced by NF-κB, has been detected in human cancers such as laryngeal squamous cell carcinoma and estrogen receptor-negative breast cancer.[30,31] NF-κB promotes angiogenesis, which is essential for tumor development, by enhancing the expression of VEGF and IL-8 .7,8,[32–34] In addition, inactivation of NF-κB has been contributed to increased apoptosis induced by chemotherapeutic agent in human breast cancer cells.[35] NF-κB inhibition also resulted in cancer growth inhibition in non-small cell lung carcinoma.[36] Similarly, a NF-κB inhibitor, Parthenolide, was capable to suppress tumor growth and enhanced response to chemotherapy in gastric cancer.[37] This findings indicate a role of NF-κB in development or progression of these types of cancer. Increased expression of NF-κB and COX-2 has been detected in cells exposed to inflammation and in malignant cells when compared to normal esophageal mucosa.[38] In addition, expression of NF-κB and COX-2 has been demonstrated in gastric cancer cells, and treatment with COX-2 inhibitors suppressed cell growth, indicating their roles in gastric cancer growth. Use of aspirin and other nonsteroidal anti-inflammatory drugs has been related to reduce risk of esophageal and gastric cancer.[38–41] Decreased expression of COX-2 and prostaglandin synthesis in esophageal squamous cell carcinoma cells treated with aspirin was associated with induction of apoptosis and reduced cell proliferation,[42] suggesting a crucial role for COX-2 in tumor cell progression. NF-κB activation was also linked to higher expression of IL-6 and VEGF in gastric carcinoma cells compared to normal mucosa.[43] NF-κB also controls the expression of apoptosis-promoting cytokines, such as TNF-α (Zhu et al., 2000), and FAS ligand (FASL).[44]

Lipopolysaccharide (LPS), a bacterial cell wall component, can increase tumor growth and NF-κB activation is required for LPS-induced tumor growth. TNF-α is involved in LPS-induced tumor growth and NF-κB activation.[45] Helicobacter pylori infection in human populations and its association with gastric cancers, Helicobacter pylori (H. pylori) is a gram-negative curved bacillus that has the ability to inhabit in the interface between mucosa and the gastric epithelium. In North American and North European populations, about one-third of adults are infected with this bacterium. In South America, South and East Europe, and Asia, the prevalence of H. pylori is estimated to be higher than 50%.[46] Gastric cancer remains the third most common cause of cancer death worldwide. In several studies, the effect of H. pylori infection on the risk of gastric cancer development has been investigated. Chronic H. pylori Infection has been etiologically linked to gastric adenocarcinoma, especially non-cardia type (63% of all stomach cancer), and to gastric mucosal associated lymphoid tissue (MALT) lymphoma, which accounts for up to 8% of all non-Hodgkin lymphoma.[47] Evidences from animal models showing H. pylori roles in gastric cancer development. In animal models, gastric H. pylori infection has been promoted experimentally induced gastric cancer development.[48] Higher gastritis score, increase in the number of Ki-67 positive (proliferative) cells, overexpression of p53 protein, and p53 gene mutation were observed in gastric mucosa infected with H. pylori in the Japanese Monkey Model.[49] In Mongolian gerbil model, H. pylori infection strongly enhanced gastric carcinogenesis initiated with a chemical carcinogen. Furthermore, eradication of H. pylori infection led to regression of inflammation and reduced the enhancing effect of H. pylori on carcinogenesis.[50] Higher scores of infiltration of inflammatory cells, hyperplasia, intestinal metaplasia, higher levels of serum anti-H. pylori IgG titer and gastrin, as well as upregulation of mucosal IL-1β, TNF-α, COX-2, and inducible nitric oxide synthase (iNOS) were observed in H. pylori-infected Mongolian gerbils.[51] Upregulation of H. pylori-induced cytokines can be linked to chronic inflammation and carcinogenesis. For example, over expression of IL-1β in the stomach of transgenic mice resulted in lower amounts of gastric acid production and these mice developed severe gastritis, atrophy, intestinal metaplasia, dyplasia and adenocarcinoma.[52] H. pylori-induces gastric inflammation and carcinogenesis, In several studies, the effect of H. pylori infection on the risk of gastric cancer development has been investigated. In a case-control study, increased H. pylori density in the corpus and infiltration of polymorphonuclear cells in the antrum were observed in patients with diffuse-type cancers. Severe chronic gastritis induced by H. pylori ¬infection has been associated with diffuse-type gastric cancer.[53] H. pylori¬ triggers inflammatory response which is characterized by secretion of proinflammatory mediators.51 Several inflammatory cytokines such as IL-1β, IL-6, IL-8, and TNF-α are secreted by gastric epithelial cells infected with ¬H. pylori in vivo (Crabtree et al., 1991; 1994). Association between the proinflammatory IL-1 gene polymorphism and H. pylori¬ infection in gastric carcinogenesis has been reported.[54] Association of ¬H. pylori with gastric cancer in patients was strong when antibodies specific to the bacterium were detected in serum collected 10 or more years before gastric cancer diagnosis (Helicobacter and Cancer Collaborative Group). Presence of the cytotoxin associated gene A (CagA) in H. pylori was linked to a higher risk for gastric cancer, whereas CagA- H. pylori infection was not

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associated with the severity of gastric lesions.55 Cag proteins have been detected in around 60% of H. pylori strains isolated in Western countries and about 95% of isolates from East Asia.[56] CagA is delivered from H. pylori into gastric epithelial cells via the bacterial type IV secretion system and activates the SHP2 phosphatase, an oncoprotein that is associated with human malignancies.[57] CagA also disrupts the tight junctions between epithelial cells by binding and inhibiting the PAR1/MARK kinase, which has an important role in epithelial cell polarity, and thereby causes loss of apical-basolateral polarity in epithelial cells.[58] In addition, CagA is contributed to the inactivation of the tumor suppressor protein p53 in gastric epithelial cells.[59] In patients infected with CagA$^+$ H. pylori strains, T helper 1 (Th1)-mediated cellular immunity was attributed to earlier stages of gastric carcinogenesis, while Th2-meiated humoral immunity was associated with the advanced stages.[55] Analysis of CagA in H. pylori strains from patients with contrasting gastric cancer suggests that CagA can be used as a biomarker for disease severity.[60] H. pylori has also a vacuolating cytotoxin (VacA) which is contributed to the free passage of urea through epithelial cells and induces vacuole formation in epithelial cells.[61] So far, there is no evidence showing a possible role for VacA in carcinogenesis. H. pylori¬-induced NF-κB activation and its role in gastric cancer development/progression, H. pylori strains carrying the cytotoxin-associated gene pathogenicity island (cagPAI) induce transcription factor NF-κB, but CagA and VacA are dispensable for direct activation of NF-κB.23 Increased activation of NF-κB and its downstream proteins, followed by increased expression of IL-8 has been demonstrated in gastric epithelial cells infected with H. pylori¬.[62] Pretreatment with a NF-κB inhibitor, PDTC, resulted in decreased H. pylori-activated p65 and IL-8.62 H. pylori¬ induced ¬NF-κB-mediated expression of IL-8 and COX-2 in gastric epithelial cells in vitro.[33] ¬H. pylori also promoted gastric cancer cell invasion through a NF-κB and COX-2-mediated pathway.[63] Furthermore, up regulation of VEGF, COX-2, and MMP-9 was detected in gastric cell lines exposed to ¬H. pylori.[64] H. pylori colonization has been detected in 36.8% of gastric carcinoma samples and expression of COX-2, beta-catenin, and VEGF, and micro vessel density were significantly higher in H. pylori-positive gastric cancer tissues than in H. pylori-negative gastric cancer tissues. H. pylori infection was also correlated with the depth of tumor invasion, lymph node metastases, and tumor-node-metastasis stage.[18] Overexpression of COX-2 protein was detected in 84% (27 of 32) gastric cancer specimens. COX-2 protein levels were significantly higher in gastric cancer specimens with CagA$^+$ H. pylori¬ infection compared to specimens without CagA$^+$ H. pylori¬ infection.[65] H. pylori infection upregulates VEGF in vitro, which is mediated by COX-2 via activation of Wnt/beta-catenin pathway.[19] Upregulation of COX-2 mRNA and enhanced prostaglandin E2 (PGE2) synthesis has been detected in human neutrophils stimulated with H. pylori. A NF-κB inhibitor and a mitogen-activated protein (MAP) kinase inhibitor significantly suppressed the COX-2 gene expression and PGE2 synthesis in the neutrophils.[66] LPS from H. pylori also promoted IL-8 secretion from human monocytes through MAP kinases and NF-κB activation.[34] In addition, gastric mucosa of patients infected with CagA$^+$ H. pylori showed higher production of reactive oxygen metabolites and greater neutrophil counts than that infected with CagA- ¬H. pylori.[67] On the other hand, human gastric epithelial cells exposed to CagA$^+$ ¬H. pylori strains increased activity of reactive oxygen species(ROS)-scavenging enzymes, including catalase, glutathione peroxidase and superoxide dismutase, and reduced susceptibility to lethal injury from ROS when compared with exposure to CagA- . pylori strains.[68] However, production of ROS and oxidative DNA damage in gastric mucosa was significantly higher in patients with CagA$^+$ H. pylori ¬infection as compared to ¬H. pylori-negative patients.[69] It has been shown that intestinal type gastric carcinoma is strongly associated with high expression of c-myc, cyclinD1 and bcl-xl genes concomitant with NF-κB/p65 in the gastric tissues infected with CagA$^+$ H. pylori.[70]

Integrin-linked kinase (ILK) is involved in cell-matrix interactions, cytoskeletal organization, and cell signaling. ILK is also contributed to carcinogenesis and progression of cancers.[71,72] ILK-mediated activation of NF-κB has been detected during H. pylori infection in macrophages and gastric cancer cells. ILK was also required for LPS-induced activation of NF-κB and TNF-α transcription and TNF-α secretion from macrophages.[73]

H. pylori LPS induces IL-1β gene expression in macrophages through activation of NF-κB and C/EBPbeta. H. pylori LPS also induces caspase-1 activation, which is essential for maturation of pro-IL-β and its release from macrophages.[74] The stimulation of TLR4 by LPS induces release of proinflammatory cytokines.[75] Furthermore, TLR4-induced signaling cascade is required for NF-κB activation and TLR polymorphisms may be responsible for clinical consequences of H. pylori infection.[76]

Increased frequency of regulatory T cells in gastric inflammation and their link with H. pylori-induced gastric cancer

In a mouse model of H. pylori ¬infection, noticeable gastric Foxp3$^+$ regulatory T cell response was induced in ¬H. pylori-infected mice, which was increased over several months together with the severity of gastric inflammation. Systemic in vivo depletion of regulatory T cells by an anti-CD25 monoclonal antibody led to increased gastric inflammation, manifested by elevated gene expression of IL-12, interferon-gamma (IFN-γ), TNF-α, IL-6, IL-10, and transforming growth factor-beta (TGF-β), and enhanced numbers of mucosal T cells, B cells, and macrophages. Depletion of CD25$^+$ T cells also reduced H. pylori colonization densities in stomach.[77] Large numbers of Foxp3$^+$ T cells were also detected in helicobacter-infected patients, but not in uninfected individuals. Increased number of CD25$^+$Foxp3$^+$ regulatory T cells in H. pylori-associated gastritis was correlated with the grade of gastric chronic inflammation. In addition, levels of Foxp3$^+$ T cells in gastric adenocarcinoma were significantly higher than those in chronic gastritis and gastric dysplasia.[78] Higher numbers of CD4$^+$FOXP3$^+$ T cells were also found in areas of duodenal gastric metaplasia in duodenal ulcer patients. Increased frequency of CD4$^+$FOXP3$^+$ T cells was observed in ¬H. pylori-infected gastric mucosa. Furthermore, eradication therapy reduced FOXP3 and IL-10 mRNA levels in the antrum, indicating that increased FOXP3$^+$ T cells in the antrum was dependent on the presence of H. pylori.[79] Increased number of CD4$^+$CD25$^+$Foxp3$^+$ T cells were also detected in patients with gastritis, patients with peptic ulcer, and patients with gastric cancer. Increased number of regulatory T cells was associated with inflammation, lymphoid follicle number, and H. pylori infection. But, regulatory T cells were negatively associated with intestinal metaplasia in gastritis and peptic ulcer groups.[80] Increased frequency of regulatory T cells have been detected in different types of cancer and they can be responsible for suppression of antitumor immune responses. But, in some types of cancer regulatory T cells may be beneficial.[81] More studies are needed to elucidate their roles in gastric cancer.

NSAIDs may reduce gastric cancer risk

In a case-control study, use of NSAIDs was associated with reduced risk of gastric and esophageal cancers.[82] In a prospective, nested case

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control study, long term use of non-aspirin NSAIDs was attributed to a reduced risk of gastric and esophageal cancers. Long-term users of aspirin were at reduced risks of esophageal cancer, but no reduction in risk was found for gastric cancer.[83] In another study, NSAID use was associated with a decreased risk of gastric cancer in a dose-dependent manner.[84] Findings from a meta-analysis suggest that long-term (≥4 years) and low-frequency (1-4.5 times per week) utilization of aspirin is associated with a significant and dose-dependent decrease in gastric cancer risk.[85] In a recent meta-analysis of observational studies, aspirin use was associated with reduced risk of esophageal, gastric, colorectal, pancreatic, endometrial, ovarian, breast, prostate cancers, and small intestinal neuroendocrine tumors. Non-significant associations were found between aspirin utilization and the risk of brain, head and neck, lung, hepato-biliary, thyroid, cervical uterus, renal, renal pelvis and urethra, bladder, and skin cancers, as well as lymphoma, and leukemia.[86]

Conclusion

Chronic infection is a risk factor for development of some types of cancer, especially gastrointestinal cancers. Immune cells as well as inflamed non-immune cells and their cytokines, chemokines and other secreted components modulate the growth, differentiation, and migration of many cell types. Certain cytokines and inflammatory mediators induced during bacterial infection can promote cancer cell proliferation and survival. Identification of molecular mechanisms involved in bacterial-induced tumor cell proliferation, survival, and invasiveness is of great importance and may result in development of new therapeutic strategies. Chronic ¬H. pylori infection can lead to gastric mucosa ulceration and inflammatory responses. This bacterium can affect host's cell survival and proliferation and also cause immunosuppression. Subsequently, progression to gastric cancer may be occurred in a smaller proportion of subjects. Induction of oxidative stress and NF-κB pathway activation may result in carcinogenesis in H. pylori¬ infected patients. Although H. pylori is a common pathogenic bacterium in the human stomach, however, most subjects with H. pylori infection will not develop gastric cancer, indicating that other factors such as genetic susceptibility of the individuals and peripheral factors are also attributed to gastric cancers. Prevention of chronic infection and inflammation is required to inhibit or decrease the development of gastric cancer.

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Conflicts of interest

The author declares that there are no conflicts of interest.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394–424.
2. Gatenby R, Brown J. Mutations, evolution and the central role of a self-defined fitness function in the initiation and progression of cancer. *Biochim Biophys Acta*. 2017;1867(2):162–66.
3. Parkin DM. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer*. 2006;118(12):3030–3044.
4. Zur Hausen H. The search for infectious causes of human cancers: where and why. *Virology*. 2009;392(1):1–10.
5. Byun MS, Jeon KI, Choi JW, et al. Dual effect of oxidative stress on NF-**k**B activation in HeLa cells. *Exp Mol Med*. 2002;34(5):332–339.
6. Naumann M. Nuclear factor-kappa B activation and innate immune response in microbial pathogen infection. *Biochem Pharmacol*. 2000;60(8):1109–1114.
7. Karin M, Lin A. NF-kappaB at the crossroads of life and death. *Nat Immunol*. 2002;3(3):221–227.
8. Kang MR, Kim MS, Kim SS, et al. NF-kappaB signalling proteins p50/p105, p52/p100, RelA, and IKKepsilon are over-expressed in oesophageal squamous cell carcinomas. *Pathology*. 2009;41(7):622–625.
9. Guttridge DC, Albanese C, Reuther JY, et al. NF-Kappa B controls cell growth and differentiation through transcriptional regulation of cyclin D1. *Mol Cell Biol*. 1999;19(8):5785–5799.
10. Chen C, Edelstein LC, Gelinas C. The Rel/NF-Kappa B family directly activates expression of the apoptosis inhibitor Bcl-x(L). *Mol Cell Biol*. 2000;20(8):2687–2695.
11. Kucharczak J, Simmons MJ, Fan Y, et al. To be, or not to be: NF-KappaB is the answer-role of Rel/NF-kappaB in the regulation of apoptosis. *Oncogene*. 2003;22(56):8961–8982.
12. Ke J, Long X, Liu Y, et al. Role of NF-kappaB in TNF-alpha-induced COX-2 expression in synovial fibroblasts from human *TMJ J Dent Res*. 2007;86(4):363–367.
13. Lim JW, Kim H, Kim KH. Nuclear factor-kappaB regulates cyclooxygenase-2 expression and cell proliferation in human gastric cancer cells. *Lab Invest*. 2001;81(3):349–360.
14. Sobolewski C, Cerella C, Dicato M, et al. The role of cyclooxygenase-2 in cell proliferation and cell death in human malignancies. *Int J Cell Biol*. 2010;2010:215158.
15. Lee EJ, Choi EM, Kim SR, et al. Cyclooxygenase-2 promotes cell proliferation, migration and invasion in U2OS human osteosarcoma cells. *Exp Mol Med*. 2007;39(4):469–476.
16. Lin C, Crawford DR, Lin S, et al. Inducible COX-2-dependent apoptosis in human ovarian cancer cells. *Carcinogenesis*. 2011;32(1):19–26.
17. Yao L, Liu F, Hong, et al. The function and mechanism of COX-2 in angiogenesis of gastric cancer cells. *J Exp Clin Cancer Res*. 2011;30(1):13.
18. Liu N, Zhou N, Chai N, et al. Helicobacter pylori promotes angiognesis depending on Wnt/beta-catenin-mediated vascular endothelial growth factor via the cyclooxygenase-2 pathway in gastric cancer. *BMC Cancer*. 2016;16:321.
19. Liu B, Qu L, Yan. Cyclooxygenase-2 promotes tumor growth and suppresses tumor immunity. *Cancer Cell Int*. 2015;15:106.
20. Rinkenbaugh A, Baldwin A. The NF-κB pathway and cancer stem cells. *Cells*. 2016;5:16.
21. Prasad S, Ravindran J, Aggarwal BB. NF-kappaB and cancer: how intimate is this relationship. *Mol Cell Biochem*. 2010;336(1-2):25–37.
22. Gambhir S, Vyas D, Hollis M, et al. Nuclear factor kappa B role in inflammation associated gastrointestinal malignancies. *World J Gastroenterol*. 2015;21:3174–3183.
23. Sokolova O, Naumann M. NF-κB Signaling in Gastric Cancer. *Toxins (Basel)*. 2017;9(4):119.
24. Verstrepen L, Bekaert T, Chau TL, et al. TLR-4, IL-1R and TNF-R signaling to NF-kappaB: variations on a common theme. *Cell Mol Life Sci*. 2008.65(19):2964–2978.
25. Senftleben U, Cao Y, Xiao G, et al. Activation by IKKalpha of a second, evolutionary conserved, NF-KAPPAB *signaling pathway Science*. 2001;293(5534):1495–1499.
26. Baud V, Karin M. Signal transduction by tumor necrosis factor and its relatives. *Trends Cell Biol*. 2001;11(9):372–377.

27. Bonizzi G, Karin M. The two NF-KAPPAB activation pathways and their role in innate and adaptive immunity. *Trends Immuno*l. 2004;25(6):280–288.

28. Mori N, Fujii M, Cheng G, et al. Human T-cell leukemia virus type I tax protein induces the expression of anti-apoptotic gene Bcl-xL in human T-cells through nuclear factor-kappaB and c-AMP responsive element binding protein pathways. *Virus Genes.* 2001;22(3):279–287.

29. Chiao PJ, Na R, Niu J, et al. Role of Rel/NF-kappaB transcription factors in apoptosis of human hepatocellular carcinoma cells. *Cancer*. 2002;95(8):1696–1705.

30. Yu Z, Wang W. The expressions of telomerase activity and cyclinD1 protein in laryngeal squamous cell carcinoma. *Linchuang Erbiyanhouke Zazhi*. 2002;16(6):286–288.

31. Umekita Y, Ohi Y, Sagara Y, et al. Overexpression of cyclinD1 predicts for poor prognosis in estrogen receptor-negative breast cancer patients. *Int J Cancer*. 2002;98(3):415–418.

32. Keates S, Hitti YS, Upton M, et al. Helicobacter pylori infection activates NF-kappa B in gastric epithelial cells. *Gastroenterology*. 1997;113(4):1099–1109.

33. Kim H, Lim JW, Kim KH. Helicobacter pylori-induced expression of interleukin-8 and cyclooxygenase-2 in AGS gastric epithelial cells: mediation by nuclear factor-kappaB. *Scand J Gastroenterol*. 2001;36(7):706–716.

34. Bhattacharyya A, Pathak S, Datta S, et al. Mitogen-activated protein kinases and nuclear factor-kappaB regulate Helicobacter pylori-mediated interleukin-8 release from macrophages. *Biochem J*. 2002;368(Pt 1):121–129.

35. Rahman KM, Ali S, Aboukameel A, et al. Inactivation of NF-KAPPAB by 3,3'-diindolylmethane contributes to increased apoptosis induced by chemotherapeutic agent in breast cancer cells. *Mol Cancer Ther*. 2007;6(10):2757–2765.

36. Tew GW, Lorimer EL, Berg TJ, et al. SmgGDS regulates cell proliferation, migration, and NF-KAPPAB transcriptional activity in non-small cell lung carcinoma. *J Biol Chem*. 2008;283(2):963–976.

37. Sohma I, Fujiwara Y, Sugita Y, et al. Parthenolide, an NF-κB inhibitor, suppresses tumor growth and enhances response to chemotherapy in gastric cancer. *Cancer Genomics Proteomics*. 2011;8(1):39–47.

38. Konturek PC, Nikiforuk A, Kania J, et al. Activation of NFkappaB represents the central event in the neoplastic progression associated with Barrett's esophagus: a possible link to the inflammation and overexpression of COX-2, PPARgamma and growth factors. *Digest Dis Sci.* 2004;49(7–8):1075–1083.

39. Lim JW, Kim H, Kim KH. Expression of Ku70 and Ku80 mediated by NF-kappa B and cyclooxygenase-2 is related to proliferation of human gastric cancer cells. *J Biol Chem*. 2002;277(48):46093–46100.

40. Liu XJ, Chen ZF, Li HL, et al. Interaction between cyclooxygenase-2, Snail, and E-cadherin in gastric cancer cells. *World J Gastroenterol*. 2013;19(37):6265–6271.

41. Farrow DC, Vaughan TL, Hansten PD, et al. Use of aspirin and other nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric cancer. *Cancer Epidemiol Biomarkers Prev*. 1998;7(2):97–102.

42. Liu JF, Jamieson GG, Drew PA, et al. Aspirin Induces Apoptosis in Oesophageal Cancer Cells by Inhibiting the Pathway of NF-kappaB Downstream Regulation of Cyclooxygenase-2. *ANZ J Surg*. 2005;75(11):1011–1016.

43. Yin Y, Si X, Gao Y, et al. The nuclear factor-κB correlates with increased expression of interleukin-6 and promotes progression of gastric carcinoma. *Oncol Rep*. 2013;29(1):34–38.

44. Hsu SC, Gavrilin MA, Lee HH, et al. NF-kappa B-dependent Fas ligand expression. Eur J Immunol. 1999;29(9):2948–2956.

45. Luo JL, Maeda S, Hsu LC, et al. Inhibition of NF-kappaB in cancer cells converts inflammation- induced tumor growth mediated by TNFalpha to TRAIL-mediated tumor regression. *Cancer Cell*. 2004;6(3):297–305.

46. Eusebi LH, Zagari RM, Bazzoli F. Epidemiology of Helicobacter pylori infection. *Helicobacter*. 2014;19 Suppl 1:1–5.

47. Mbulaiteye SM, Hisada M, El Omar EM. Helicobacter Pylori associated global gastric cancer burden. *Front Biosci*. 2009;14:1490–1504.

48. Watanabe T, Tada M, Nagai H, et al. Helicobacter pylori infection induces gastric cancer in Mongolian gerbils. *Gastroenterology*. 1998;115(3):642–648.

49. Fujioka T, Murakami K, Kodama M, et al. Helicobacter pylori and gastric carcinoma--from the view point of animal model. *Keio* J Med. 2002;51 Suppl 2:69–73.

50. Nozaki K, Shimizu N, Ikehara Y, et al. Effect of early eradication on Helicobacter pylori-related gastric carcinogenesis in Mongolian gerbils. *Cancer Sci*. 2003;94(3):235–239.

51. Cao X, Tsukamoto T, Nozaki K, et al. Severity of gastritis determines glandular stomach carcinogenesis in Helicobacter pylori-infected Mongolian gerbils. *Cancer Sci*. 2007;98(4):478–483.

52. Shuiping Tu, Govind Bhagat, Guanglin Cui, et al. Overexpression of interleukin-1beta induces gastric inflammation and cancer and mobilizes myeloid-derived suppressor cells in mice. *Cancer Cell*. 2008;14(5):408–419.

53. Fukuda S, Tanaka M, Soma Y, et al. Histological analysis of gastritis and Helicobacter pylori infection in patients with early gastric cancer: a case-control study. *J Gastroenterol Hepatol*. 2000;15(12):1370–1376.

54. Li C, Xia HH, Xie W, et al. Association between interleukin-1 gene polymorphisms and Helicobacter pylori infection in gastric carcinogenesis in a Chinese population. *J Gastroenterol Hepatol*. 2007;22(2):234–239.

55. Wang SK, Zhu HF, He BS, et al. CagA+ H pylori infection is associated with polarization of T helper cell immune responses in gastric carcinogenesis. *World J Gastroenterol.* 2007;13(21):2923–2931.

56. Yamazaki S, Yamakawa A, Okuda T., et al. Distinct diversity of vacA, cagA, and cagE genes of Helicobacter pylori associated with peptic ulcer in Japan. *J Clin Microbiol*. 2005;43(8):3906–3916.

57. Hatakeyama M. Oncogenic mechanisms of the Helicobacter pylori CagA protein. *Nat Rev Cancer*. 2004;4(9):688–694.

58. Saadat I, Higashi H, Obuse C, et al. Helicobacter pylori CagA targets PAR1/MARK kinase to disrupt epithelial cell polarity. *Nature*. 2007;447(7142):330–333.

59. Wei J, Nagy TA, Vilgelm A, et al. Regulation of p53 tumor suppressor by Helicobacter pylori in gastric epithelial cells. *Gastroenterology*. 2010;139(4):1333–1343.

60. Loh JT, Shaffer CL, Piazuelo MB, et al. Analysis of cagA in Helicobacter pylori strains from Colombian populations with contrasting gastric cancer risk reveals a biomarker for disease severity. Cancer *Epidemiol Biomarkers Prev*. 2011; 20(10):2237–2249.

61. Marshall B. Helicobacter pylori: 20 years on. *Clin Med*. 2002;2(2):147–152.

62. Keates S, Hitti YS, Upton M, et al. Helicobacter pylori infection activates NF-kappa B in gastric epithelial cells. *Gastroenterology*. 1997;113(4):1099–1109.

63. Wu CY, Wang CJ, Tseng CC, et al. Helicobacter pylori promote gastric cancer cells invasion through a NF-kappaB and COX-2-mediated pathway. *World J Gastroenterol*. 2005;11(21):3197–3203.

64. Han JC, Kai-Li Zhang, Xiao-Yan Chen, et al. Expression of Seven Gastric Cancer-associated Genes and Its Relevance for Wnt, NF-κB and Stat3 Signaling. *Apmis*. 2007;115(12):1331–1343.

Citation: Bonab SF, Khansari N. Role of bacterial infection in the development and progression of gastric cancers. *MOJ Immunol.* 2018;6(6):316–321. DOI: 10.15406/moji.2018.06.00251

65. Guo Y, Xu F, Lu T, et al. Interleukin-6 signaling pathway in targeted therapy for cancer. *Cancer Treat Rev*. 2012;38(7):904–910.

66. Kim JS, Kim JM, Jung HC, et al. Expression of cyclooxygenase-2 in human neutrophils activated by Helicobacter pylori water-soluble proteins: possible involvement of NF-kappaB and MAP kinase signaling pathway. *Dig Dis Sci*. 2001;46(10):2277–2284.

67. Danese S, Cremonini F, Armuzzi A, et al. Helicobacter pylori CagA-positive strains affect oxygen free radicals generation by gastric mucosa. *Scand J Gastroenterol*. 2001;36(3):247–250.

68. Smoot DT, Elliott TB, Verspaget HW, et al. Influence of Helicobacter pylori on reactive oxygen-induced gastric epithelial cell injury. *Carcinogenesis*. 2000;21(11):2091–2095.

69. Papa A, Danese S, Sgambato A, et al. Role of Helicobacter pylori CagA+ infection in determining oxidative DNA damage in gastric mucosa. *Scand J Gastroenterol*. 2002;37(4):409–413.

70. Yang GF, Deng CS, Xiong YY, et al. Expression of nuclear factor-kappa B and target genes in gastric precancerous lesions and adenocarcinoma: association with Helicobactor pylori cagA (+) infection. *World J Gastroenterol*. 2004;10(4):491–496.

71. Fielding AB, Lim S, Montgomery K, et al. A critical role of integrin-linked kinase, ch-TOG and TACC3 in centrosome clustering in cancer cells. *Oncogene*. 2011;30(5):521–534.

72. Wani AA, Jafarnejad SM, Zhou J, et al. Integrin-linked kinase regulates melanoma angiogenesis by activating NFκB/interleukin-6 signaling pathway. *Oncogene*. 2011;30(24):2778–2788.

73. Ahmed AU, Sarvestani ST, Gantier MP, et al. Integrin-linked kinase modulates lipopolysaccharide- and Helicobacter pylori-induced nuclear factor κB-activated tumor necrosis factor-α production via regulation of p65 serine 536 phosphorylation. *J Biol Chem*. 2014;289(40):27776–27793.

74. Basak C, Pathak SK, Bhattacharyya A, et al. NF-kappaB- and C/EBPbeta-driven interleukin-1beta gene expression and PAK1-mediated caspase-1 activation play essential roles in interleukin-1beta release from Helicobacter pylori lipopolysaccharide-stimulated macrophages. *J Biol Chem*. 2005;280(6):4279–4288.

75. Lu YC, Yeh WC, Ohashi PS. LPS/TLR4 signal transduction pathway. *Cytokine*. 2008;42(2):145–151.

76. Hu Y, Liu JP, Zhu Y, et al. The Importance of Toll-like Receptors in NF-κB Signaling Pathway Activation by Helicobacter pylori Infection and the Regulators of this Response. *Helicobacter*. 2016;21(5):428–440.

77. Rad R, Brenner L, Bauer S, et al. CD25+/Foxp3+ T cells regulate gastric inflammation and Helicobacter pylori colonization in vivo. *Gastroenterology*. 2006;131(2):525–537.

78. Jang TJ. The number of Foxp3-positive regulatory T cells is increased in Helicobacter pylori gastritis and gastric cancer. *Res Pract* Pathol. 2010;206(1):34–38.

79. Kindlund B, Sjöling A, Hansson M, et al. FOXP3-expressing CD4(+) T-cell numbers increase in areas of duodenal gastric metaplasia and are associated to CD4(+) T-cell aggregates in the duodenum of Helicobacter pylori-infected duodenal ulcer patients. *Helicobacter*. 2009;14(3):192–201.

80. Cheng HH, Tseng GY, Yang HB, et al. Increased numbers of Foxp3-positive regulatory T cells in gastritis, peptic ulcer and gastric adenocarcinoma. *World J Gastroenterol*. 2012;18(1):34–43.

81. Farashi-bonab S, Khansari N. Regulatory T Cells in Cancer Patients and Their Roles in Cancer Development/Progression. *MOJ Immunol*. 2014;1(4):00024.

82. Farrow DC, Vaughan TL, Hansten PD, et al. Use of aspirin and other nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric cancer. *Cancer Epidemiol Biomarkers Prev*. 1998;7(2):97–102.

83. Lindblad M, Langergren J, García Rodríguez LA. Nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric cancer. *Cancer Epidemiol Biomarkers Prev*. 2005;14(2):444–450.

84. Wang WH, Huang JQ, Zheng GF, et al. Non-steroidal anti-inflammatory drug use and the risk of gastric cancer: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2003;95(23):1784–1791.

85. Ye X, Fu J, Yang Y, et al. Dose-risk and duration-risk relationships between aspirin and colorectal cancer: a meta-analysis of published cohort studies. *PLoS One*. 2013;8(2):e57578.

86. Qiao Y, Yang T, Gan Y, et al. Associations between aspirin use and the risk of cancers: a meta-analysis of observational studies. *BMC Cancer*. 2018;18(1):288.

Citation: Bonab SF, Khansari N. Role of bacterial infection in the development and progression of gastric cancers. *MOJ Immunol.* 2018;6(6):316–321. DOI: 10.15406/moji.2018.06.00251