From inflammation to gastric cancer: Role of Helicobacter pylori (Review)

XIAO-YING ZHANG¹, PEI-YING ZHANG² and MOURAD A.M. ABOUL-SOUD³

¹Nanjing University of Chinese Medicine, Information Institute, Nanjing; ²Department of Cardiology, Xuzhou Central Hospital, The Affiliated Xuzhou Hospital of Medical College of Southeast University, Xuzhou, Jiangsu 221009, P.R. China; ³Chair of Medical and Molecular Genetics Research, Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, King Saud University, Riyadh 11433, Kingdom of Saudi Arabia

Received July 7, 2016; Accepted December 8, 2016

DOI: 10.3892/ol.2016.5506

Abstract. Gastric cancer is a multifactorial disease and a leading cause of mortality and the risk factors for this include environmental factors and factors that influence host-pathogen interaction and complex interplay between these factors. Gastric adenocarcinomas are of two types, namely intestinal and diffuse type, and Helicobacter pylori (H. pylori) infection has been suspected of being causally linked to the initiation of chronic active gastritis, which leads to adenocarcinoma of the intestinal type. Even though most individuals with H. pylori infection do not show any clinical symptoms, long-term infection leads to inflammation of gastric epithelium and approximately 10% of infected patients develop peptic ulcers and 1-3% of patients develop gastric adenocarcinoma. Among the several mechanisms involved in tumorigenesis, CagA and peptidoglycan of H. pylori, which enter the infected gastric epithelial cells play an important role by triggering oncogenic pathways. Inflammation induced by H. pylori in gastric epithelium, which involves the cyclooxygenase-2/prostaglandin E2 pathway and IL-1β, is also an important factor that triggers chronic active gastritis and adenocarcinoma. H. pylori infection induced oxidative stress and dysregulated E-cadherin/β-catenin/p120 interactions and function also play a critical role in tumorigenesis. Environmental and dietary factors, in particular salt intake, are known to modify the pathogenesis induced by H. pylori. Gastric cancer induced by H. pylori appears to involve several mechanisms, making this mode of tumorigenesis a highly complicated process. Nevertheless, there are many events in this tumorigenesis that remain to be clarified and investigated.

Contents

1. Introduction
2. Events leading to gastric carcinogenesis following H. pylori infection
3. Inflammatory response to H. pylori infection
4. Oxidative stress induced by H. pylori
5. H. pylori and E-cadherin
6. Environmental factors and H. pylori-mediated gastric carcinogenesis
7. Conclusion

I. Introduction

Gastric cancer is a leading cause of cancer-related mortality worldwide, with nearly 1 million new cases and approximately 750,000 mortalities annually (1). Gastric cancer is a multifactorial disease and the risk factors for this include environmental factors and factors that influence host-pathogen interaction and complex interplay between these factors. Gastric cancer occurrence is more predominant in developing countries in Eastern Europe, South America, and Asia, accounting for approximately two thirds of all cases globally, with China representing approximately 42% of all new cases (2). Development of gastric cancer likely originates with the onset of chronic active gastritis and follows with atrophic gastritis, intestinal metaplasia, and dysplasia, eventually leading to gastric cancer (3). Besides environmental, diet and genetic factors, gastric cancer is closely associated with Helicobacter pylori (H. pylori) infection (4) and related host gene polymorphisms (5). Gastric adenocarcinomas constitute 90-95% of gastric cancers and are of two types, intestinal and diffuse type. Although there is no known precursor lesion for the development of diffuse type of gastric cancers, H. pylori infection has been suspected of being causally linked to the
initiation of chronic active gastritis, which leads to adenocarcinoma (6). Infection of \textit{H. pylori} is one of the thoroughly studied risk factors of gastric cancer.

After its identification in 1984, \textit{H. pylori} was classified as a type I carcinogen and epidemiological studies indicated that \textit{H. pylori} is the most common etiological agent for cancers that are related to infection (7,8). \textit{H. pylori} is a gram-negative bacterial pathogen and is colonized in gastric epithelium despite the harsh acidic environment, because of its ability to conduct urease-mediated breakdown of urea to ammonia and neutralize its surrounding environment (9). Even though most individuals with \textit{H. pylori} infection do not exhibit any clinical symptoms, long-term infection potentially leads to inflammation of gastric epithelium and approximately 10% of infected patients develop peptic ulcers and 1-3% subjects develop gastric adenocarcinoma (10,11).

In this review, we address the molecular basis by which \textit{H. pylori} acts as a carcinogen, the potential factors that enhance the risk from \textit{H. pylori} and the accumulating epidemiological evidence for \textit{H. pylori} infection and its effect on gastric cancer incidence.

2. Events leading to gastric carcinogenesis following \textit{H. pylori} infection

\textit{H. pylori} infection of gastric epithelium leads to the development of intestinal-type adenocarcinoma with the primary event being the transition from normal mucosa to chronic superficial gastritis. Subsequently, atrophic gastritis ensues followed by intestinal metaplasia, leading to dysplasia and adenocarcinoma (Fig. 1) (12). Men are twice as susceptible as women to the intestinal type of gastric adenocarcinoma (13). Notably, the location of infection and formation of gastritis influences the outcomes. Thus, corpus-predominant gastritis leads to gastric cancer, probably because of lower acid secretion, whereas, infection of the gastric antrum, which increases acid production predisposes individuals to duodenal ulcer, actually decreases the risk of gastric cancer (14).

\textit{cag} pathogenicity island and CagA. Several virulence factors present in \textit{H. pylori} that are influenced by its genetic heterogeneity, are critical in the pathogenesis of gastric cancer. CagA, which is present in the DNA insertion element, \textit{cag} pathogenicity island (cagPAI), was found to be important in carcinogenesis and thus, only \textit{H. pylori} strains that contain cagPAI element enhance the risk of atrophic gastritis and gastric cancer, even though all strains of this bacterium can cause gastritis (15,16). \textit{H. pylori} CagA is a 120 to 140-kDa protein, which translocates into host cells following attachment of the bacteria to the cell. Inside the host cell, CagA is phosphorylated by Abl and Src kinases, on tyrosine residue at four distinct glutamate-proline-isoleucine -tyrosine-alanine (EPIYA) motifs present at the C-terminal region of the protein, leading to morphological changes in the cell, including increased cell migration (17,18). The number and phosphorylation status of these EPIYA motifs is a determinant and indicator of risk for gastric cancer (19). Tyr-phospho-CagA activates tyrosine phosphatase (SHP-2) in the host cell, leading to sustained activation of ERK1/2, Crk adaptor, and C-terminal Src kinase (20). Interaction between phosphor-CagA and SHP leads to cell elongation by different mechanisms (21). Even non-phosphorylated CagA has pathogenic effects by causing aberrant activation of β-catenin, disruption of apical-junctional complexes, and a loss of cellular polarity (22). Additionally, non-phosphorylated CagA targets E-cadherin, the hepatocyte growth factor receptor c-Met, phospholipase C-γ, the adaptor protein Grb2, and other components that lead to proinflammatory and mitogenic responses, disruption of cell-cell junctions, and loss of cell polarity (Fig. 1) (23). Preclinical studies confirmed a role for CagA in the pathogenesis of gastric cancer, by demonstrating that transgenic mice expressing CagA show gastric epithelial cell proliferation and carcinoma, in a CagA phosphorylation-dependent manner (24).

Peptidoglycan. Along with CagA, \textit{H. pylori} peptidoglycan can also be delivered into host cells and peptidoglycan binds with NodI (25), which triggers the NF-κB dependent pro-inflammatory pathway and interleukin (IL)-8, an inflammatory cytokine, secretion. Peptidoglycan is also shown to activate the PI3K-Akt pathway leading to cell proliferation, migration and prevention of apoptosis (26).

Other virulence factors present in \textit{H. pylori} include VacA and outer membrane proteins, which are associated with ulceration as well as gastric cancer (27,28).

3. Inflammatory response to \textit{H. pylori} infection

\textit{COX-2/PGE2 pathway}. Inflammation of gastric epithelium is known to be associated with the development of gastric cancer (29). There are several mechanisms by which inflammation may promote cancer development and the induction of the cyclooxygenase-2/prostaglandin E2 (COX-2/PGE2) pathway and activation of NF-κB and Stat3 appear to be major pathways (Fig. 2) (30). Besides these, innate immune responses through the TLR/MyD88 adapter signaling also play a role in tumorigenesis (31,32). In fact, it has been shown that almost all the gastric tumors show an induction of COX-2 expression (33) and \textit{H. pylori} infection is known to lead to COX-2 induction (34). Inflammation in combination with oncogenic activation, promotes tumorigenesis and also Wnt signaling activation (Fig. 2) with the accumulation of β-catenin, which facilitate tumor growth and this altered signaling has been observed in over 50% of gastric cancers (35). PGE2 signaling, through the EP4 receptor, is known to induce the expansion of CD133+ CD44+ cancer stem cells in intestinal tumors through the activation of PI3K and MAPK signaling (36), which potentially aggravates tumor growth.

Infection of \textit{H. pylori} induces inflammation through CagA injection into host cells followed by the activation of SHP and TLRs leading to chronic active gastritis and eventually gastric cancer. However, the expression pattern of inflammation markers is not always comparable between gastritis and gastric cancer. Thus, IL-8 and IL-11 expression is predominantly induced in gastric cancer, whereas in gastritis mostly TNF-α expression is increased. It has been suggested that once tumor growth starts, tumor cells also contribute to the inflammation of local microenvironment through different pathways, known as 'tumor-elicited inflammation', which is different from infection-induced inflammation, thereby resulting in different cytokine profiles from \textit{H. pylori} infection-induced gastritis (29). Nevertheless, gastritis and
gastric cancer demonstrate common increases in inflammatory cytokines CXCL1, CXCL2, CXCL5, CCL3, CCL4, and TLR2 (Fig. 2) (29). Inasmuch as these cytokines are effective in causing immune suppression, the ‘infection-associated’ and ‘tumor-elicited’ inflammation appears to promote and accelerate gastric tumorigenesis by activating the COX-2/PGE2 pathway and subsequent induction of tumor-promoting cytokines.

IL-1β. Another important cytokine, IL-1β is known to play a role in a variety of cellular activities such as inflammatory response and acid secretion by gastric epithelium (37). Disturbances in the regulation of IL-1β are observed in several cancer types and in particular, in IL-1β gene polymorphisms including IL-1β -31 (T>C) and IL-1β -511 (C>T) which are closely related to gastric cancer (Fig. 1) (38,39). Of note, it has been shown that IL-1β-511T polymorphism is present in all the Mozambican subjects with intestinal metaplasia (40). This polymorphism is also associated with the prevalence of dysplasia (41), indicating that the IL-1β T alleles are related to premalignant gastric lesions. Apparently, the same polymorphism of IL-1β is involved in the intestinal type of gastric cancers, which are triggered by H. pylori infection and not diffusive type (42). IL-1β gene polymorphisms also increase the production of IL-1β, which suppresses gastric acid secretion, and is related to the grade of gastric atrophy in patients with H. pylori infection (43). Additionally, H. pylori infection leads to elevated secretion of IL-1β and reduction in acid secretion (44). It has been suggested that a combination of IL-1β-511T/T polymorphism and H. pylori infection aggravates the development of gastric tumor more than either of these agents alone (45). Thus, infection of H. pylori promotes the expression of IL-1β, which leads to gastric carcinogenesis through its actions on both inflammatory and epithelial cells (46). Even though the precise molecular basis of these actions is not clear, it seems that hypochlorhydria and atrophic gastritis induced by IL-1β polymorphisms, which depends on H. pylori infection are critical in gastric cancer development (47).

4. Oxidative stress induced by H. pylori

A primary factor that is important in the events that lead to the progression of the inflammation-to-carcinoma is oxidative DNA damage induced by H. pylori infection (48), which is

Figure 1. Interaction between host responses, changes in gastric mucosa and environment during gastric carcinogenesis induced by Helicobacter pylori (H. pylori). A combination of several host responses, bacterial pathogen-mediated events, and environmental factors contribute to the precancerous cascade that culminates in gastric adenocarcinoma.
probably due to infiltrating neutrophils, and also direct effects of \textit{H. pylori} (49). Production of reactive oxygen species in the \textit{H. pylori}-infected gastric epithelium is linked to the presence of cagPAI and contribute to the oxidative stress response in gastric epithelial cells (50). It is well known that \textit{H. pylori} infection causes elevated level of polyamines, in particular spermine and this is associated with an induction of spermine oxidase (51). Action of spermine oxidase on spermine leads to the production of elevated levels of hydrogen peroxide, which is a powerful oxidizing agent and also contributes to the production of free radicals such as hydroxyl radical (52). Besides, \textit{H. pylori} also activates macrophages which show a significant upregulation of spermine oxidase, contributing to oxidative stress and damage to the gastric epithelial cells (53). Besides, altered polyamine metabolism and overexpression of arginase enzyme in the infected gastric epithelium leads to lowered NO production and increased production of spermine and hydrogen peroxide.

5. \textit{H. pylori} and E-cadherin

E-cadherin, which is an adhesion molecule in epithelial tissues that is important in maintaining proper cellular architecture, is regulated by the binding of p120 to the cadherin juxta membrane domain (54). Furthermore, the cytoplasmic domain of E-cadherin interacts with β-catenin and p120, which, in turn, interact with the cytoskeletal component actin. It has been documented that there is a loss of E-cadherin function in gastric cancer, and in fact promoter methylation of E-cadherin gene is induced by \textit{H. pylori} infection, leading to reduction in E-cadherin expression (55). Following \textit{H. pylori} infection, the translocated CagA in the gastric epithelial cells binds with E-cadherin, resulting in the dissociation of the E-cadherin-β-catenin complex and accumulation of β-catenin in cytoplasm and nucleus, where it transactivates β-catenin-dependent genes involved in carcinogenesis (23,56). Along with the downregulation of E-cadherin, a decreased expression or aberrant subcellular localization of p120, from membrane to the cytosol or nucleus, is commonly seen in gastric cancer (57). In the cytoplasm, p120 interacts with Rho GTPases and promotes motility and metastasis (58). Aberrant localization of p120 to the nucleus in gastric epithelia infected with \textit{H. pylori} has been reported and p120 in nucleus can relieve transcriptional repression of the mmp-7 gene, which is involved in gastric tumorigenesis, leading to its enhanced expression (59).
6. Environmental factors and _H. pylori_-mediated gastric carcinogenesis

Gastric adenocarcinoma is strongly influenced by dietary salt intake, with high salt intake aggravating tumorigenesis (60). Epidemiological studies indicated that high salt intake increases the prevalence of _H. pylori_ infection (61) and the incidence of gastric adenocarcinoma in infected patients (62). Experimental studies indicated that a high-salt diet and _H. pylori_ infection exert synergistic effects on the development of premalignant lesions or gastric cancer (63), probably by elevating the production of inflammatory cytokines IL-1, IL-6 and TNF-α (64). However, the precise molecular events that underlie this synergistic effect on cancer development are not known. It has been suggested that high salt increases the expression of CagA, the potential carcinogen in _H. pylori_ (65), which may be the reason for the observed synergy between _H. pylori_ and salt for gastric cancer induction (Fig. 1). In addition to salt, other factors that influence _H. pylori_ infection-associated gastric cancer include helminth infections and dietary antioxidant intake, both of which seem to have a negative effect on the ability of _H. pylori_ to induce gastritis and thus cancer. On the other hand, cigarette smoking is a potential risk factor for enhancing the tumorigenesis induced by _H. pylori_ infection (21).

7. Conclusion

Intestinal type gastric adenocarcinomas are known to be causally linked to _H. pylori_ infection, which leads to the initiation of chronic active gastritis, and adenocarcinoma. Even though most individuals with _H. pylori_ infection do not show any clinical symptoms, 1-3% people with long-term infection develop gastric adenocarcinoma. Of the several mechanisms of the tumorigenesis induced by _H. pylori_, CagA and peptidoglycan of _H. pylori_, inflammation, oxidative stress and dysregulated E-cadherin/β-catenin/p120 interactions play an important role. Environmental and dietary factors, in particular salt intake and cigarette smoking, are known to aggravate gastric adenocarcinoma. Of the several mechanisms of the tumorigenesis induced by _H. pylori_, CagA and peptidoglycan of _H. pylori_, inflammation, oxidative stress and dysregulated E-cadherin/β-catenin/p120 interactions play an important role. Environmental and dietary factors, in particular salt intake and cigarette smoking, are known to aggravate gastric adenocarcinoma.

Nevertheless, many events in this tumorigenic process remain to be clarified and investigated.

References

1. Ferro A, Peletiero B, Malvezzi M, Bosetti C, Bertuccio P, Levi F, Negri E, La Vecchia C, Lucat N: Worldwide trends in gastric cancer mortality (1980-2011), with predictions to 2015, and incidence by subtype. Eur J Cancer 50: 1330-1344, 2014.
2. Jemal A, Bray F, Center MM, Ferlay J, Ward E and Forman D: Global cancer statistics. CA Cancer J Clin 61: 69-90, 2011.
3. Correa P: Human gastric carcinogenesis: a multistep and multifactorial process - first American cancer society award lecture on cancer epidemiology and prevention. Cancer Res 52: 6735-6740, 1992.
4. Herrera V and Parsonnet J: _Helicobacter pylori_ and gastric adenocarcinoma. Clin Microbiol Infect 15: 971-976, 2009.
5. He C, Tu H, Sun L, Xu Q, Li P, Gong Y, Dong N and Yuan Y: _Helicobacter pylori_-related host gene polymorphisms associated with susceptibility of gastric carcinogenesis: a two-stage case-control study in China. Carcinogenesis 34: 1450-1457, 2013.
6. Souza RF and Spechler SJ: Concepts in the prevention of adenocarcinoma of the distal esophagus and proximal stomach. CA Cancer J Clin 55: 334-351, 2005.
7. Marshall BJ and Warren JR: Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1: 1311-1315, 1984.
8. Parkin DM, Bray F, Ferlay J and Pisani P: Global cancer statistics, 2002. CA Cancer J Clin 55: 74-108, 2005.
9. Weeks DL, Eskandari S, Scott DR and Sachs G: A H*-gated urea channel: the link between _Helicobacter pylori_ urease and gastric colonization. Science 287: 482-485, 2000.
10. Peek RM Jr and Blaser MJ: _Helicobacter pylori_ and gastrointestinal tract adenocarcinomas. Nat Rev Cancer 2: 28-37, 2002.
11. Peek RM Jr and Crabtree JE: Helicobacter infection and gastric cancer: An overview. J Pathol 208: 233-248, 2006.
12. Sipponen P and Marshall BJ: Gastritis and gastric cancer. Western countries. Gastroenterol Clin North Am 29: 579-592, 2000.
13. Correa P and Houghton J: Carcinogenesis of _Helicobacter pylori_. Gastroenterology 133: 659-672, 2007.
14. Atherton JC: The pathogenesis of _Helicobacter pylori_-induced gastro-duodenal diseases. Annu Rev Pathol 1: 63-96, 2006.
15. Shimoyama T, Fukuda S, Tanaka M, Mikami T, Munakata A and Crabtree JE: CagA seropositivity associated with development of gastric cancer in a Japanese population. J Clin Pathol 51: 225-228, 1998.
16. Torres J, Pérez-Pérez GI, Leal-Herrera Y and Muñoz O: Infection with CagA* _Helicobacter pylori_ strains as a possible predictor of risk in the development of gastric adenocarcinoma in Mexico. Int J Cancer 78: 298-300, 1998.
17. Stein M, Bagnoli F, Halenbeck R, Rapiuoli R, Funt WL and Covacci A: c-Src/Lyn-mediated activation _Helicobacter pylori CatA_ through tyrosine phosphorylation of the EPIYA motifs. Mol Microbiol 43: 971-980, 2002.
18. Segal ED, Cha J, Lo J, Falkow S and Tompkins LS: Altered states: involvement of phosphorylated CatA in the induction of host cellular growth changes by _Helicobacter pylori_. Proc Natl Acad Sci USA 96: 14559-14564, 1999.
19. Basso D, Zambon CF, Letley DP, Stranges A, Marchet A, Rhead JL, Schiavon S, Guariso G, Ceroti M, Nitti D, et al: Clinical relevance of _Helicobacter pylori_ cagA and vacA gene polymorphisms. Gastroenterology 135: 91-99, 2008.
20. Higashi H, Tsutsumi R, Muto S, Sugiyauma T, Azuma T, Asaka M and Hatakeyama M: SHP-2 tyrosine phosphatase as an intra-cellular target of _Helicobacter pylori_ CatA protein. Science 295: 683-686, 2002.
21. Wrobleski LE, Peek RM Jr and Wilson KT: _Helicobacter pylori_ and gastric cancer: factors that modulate disease risk. Clin Microbiol Rev 23: 713-739, 2010.
22. Bagnoli F, Buti L, Tompkins LS, Covacci A and Amievra MR: _Helicobacter pylori_ CatA induces a transition from polarized to invasive phenotypes in MDCK cells. Proc Natl Acad Sci USA 102: 16339-16344, 2005.
23. Murata-Kamiya N, Kurashima Y, Teishikata Y, Yamashita Y, Saito Y, Higashi H, Aburatani H, Akiyama T, Peek RM Jr, Azuma T, et al: _Helicobacter pylori_ CatA interacts with E-cadherin and deregulates the beta-catenin signal that promotes intestinal transdifferentiation in gastric epithelial cells. Oncogene 26: 4617-4626, 2007.
24. Ohnishi N, Yuasa H, Tanaka S, Sawa H, Maira M, Matsui A, Higashi H, Musashi M, Iwabuchi K, Suzuki M, et al: Transgenic expression of _Helicobacter pylori_ CatA induces gastrointestinal and hematopoietic neoplasms in mouse. Proc Natl Acad Sci USA 105: 1003-1008, 2008.
25. Viala J, Chaput C, Boneca IG, Cardona A, Girardin SE, Moran AP, Athman R, Ménet S, Huerre MR, Coyle AJ, et al: Nod1 responds to peptidoglycan delivered by the _Helicobacter pylori_ cag pathogenicity island. Nat Immunol 5: 1164-1174, 2004.
26. Nagy TA, Frey MR, Yan F, Israel DA, Polk DB and Peek RM Jr: _Helicobacter pylori_ regulates cellular migration and apoptosis by activation of phosphatidylinositol 3-kinase signaling. J Infect Dis 199: 641-651, 2009.
27. Mielke S, Kirsch C, Aghiari A, Günther K, Lern N, Malfertheiner P, Stolte M, Eberinger G and Bayerdörffer E: The _Helicobacter pylori_ vacA s1, m1 genotype and cagA is associated with gastric carcinoma in Germany. Int J Cancer 87: 322-327, 2000.
28. Dossoumveka O, Prinz C, Gerhard M, Brenner L, Backert S, Kallings LG, Schwall KF and Raitt R: _Helicobacter pylori_ outer membrane proteins and gastric inflammation. Gut 55: 1360-1361, 2006.
infection induces oxidative stress and associated premalignant and malignant gastric lesions. Myeloid results in apoptosis: First-degree relatives of early-onset gastric-induced gastric lesions, cell proliferation, induced Spermine 47. 46. 44. 43. 42. 40. 39. 38. 35. 34. 33. 31. 30. 29. 548 [57x110]
Ding SZ, Minohara Y, Fan XJ, Wang J, Reyes VE, Patel J, Dirden-Kramer B, Boldogh I, Ernst PB and Crowe SE: Helicobacter pylori infection induces oxidative stress and programmed cell death in human gastric epithelial cells. Infect Immun 75: 4030-4039, 2007.
Cheng Y, Chaturvedi R, Asim M, Bussièere FI, Scholz A, Xu H, Casero RA Jr and Wilson KT: Helicobacter pylori-induced macrophage apoptosis requires activation of ornithine decarboxylase by c-Myc. J Biol Chem 280: 22492-22496, 2005.
Xu H, Chaturvedi R, Cheng Y, Bussièere FI, Asim M, Yao MD, Potosky D, Meltzer SJ, Rhee JG, Kim SS, et al: Spermine oxidation induced by Helicobacter pylori results in apoptosis and DNA damage: implications for gastric carcinogenesis. Cancer Res 64: 8521-8525, 2004.
Chaturvedi R, Cheng Y, Asim M, Bussièere FI, Xu H, Gobert AP, Hacker A, Casero RA Jr and Wilson KT: Induction of polyaniline ox1 by Helicobacter pylori causes macrophage apoptosis by hydrogen peroxide release and mitochondrial membrane depolarization. J Biol Chem 279: 40167-40175, 2004.
Peleteiro B, Lunet N, Carrilho C, Durães C, Machado JC, Seruca R, Mareel M and Figueiredo C: CagA associates with c-Met, E-cadherin, and p21 expression in Mongolian gerbils. Dig Dis Sci 52: 180-185, 1999.
Mayo JK, Parkman PH, Kessler KM, Fehn M and Garza-González E: Role of the polymorphic IL-1B, IL-1RN and TNF-A pathway. Gastroenterology 131: 1086-1095, 2006.
Kumar S, Kumar A and Dixit VK: Evidences showing association of interleukin-1B polymorphisms with increased risk of gastric cancer in an Indian population. Biochem Biophys Res Commun 387: 456-460, 2009.
Zhang et al: FROM INFLAMMATION TO GASTRIC CANCER: ROLE OF Helicobacter pylori infection enhances mouse gastric carcinogenesis. J Cancell 340 (Suppl 11): 10-17, 1999.
Zeng ZR, Hu PJ, Hu S, Pang RP, Chen MH, Ng M and Sung JJ: Altered expression of matrix metalloproteinase-7. Mol Biol Cell 15: 391-397, 2004.
Tijerina-Menchaca R, Maldonado-Garza HJ and Pérez-Pérez GI: Interleukin-1beta promotes gastric atrophy through suppression of the src substrate p120(ctn) in gastric carcinoma. J Pathol 189: 237-241, 2005.
Kumar S, Kumar A and Dixit VK: Evidences showing association of interleukin-1B polymorphisms with increased risk of gastric cancer in an Indian population. Biochem Biophys Res Commun 387: 456-460, 2009.
Garza-González E, Bosques-Padilla JF, El-Omar E, Hold G, Tijerina-Menacho R, Maldonado-Garza HJ y Pérez-Pérez GI: Role of the polymorphic IL-1B, IL-1RN and TNF-A genes in distal gastric cancer in Mexico. Int J Cancer 114: 237-241, 2005.
Peleteiro B, Lunet N, Carrilho C, Durães C, Machado JC, La Vecchia C and Barros H: Inflammation and Toll-like receptor/MyD88 pathways. Cancer Sci 107: 650-657, 2006.
Peleteiro B, Lunet N, Carrilho C, Durães C, Machado JC, Seruca R, Mareel M and Farthing M: Up-regulated cytoplasmic expression, with reduced membranous distribution, of the src substrate p120(ctn) in gastric carcinoma. J Pathol 189: 180-185, 1999.
Noren NK, Liu BP, Burridge K and Kreft B: p120 catenin regulates the actin cytoskeleton via Rho family GTPases. J Cell Biol 150: 567-580, 2000.
Ogden SR, Wroblewski LE, Weydig C, Romero-Gallo J, O’Brien DP, Israel DA, Krishna US, Fingleton B, Reynolds AB, Wessler S, et al: p120 and Kaiso regulate Helicobacter pylori-induced expression of matrix metalloproteinase-7. Mol Biol Cell 19: 4110-4121, 2008.
Sugimura H: Interleukin 1beta polymorphisms increase risk of duodenal ulcer recurrence in Japan. Gastroenterology 123: 92-105, 2002.