New insights of *Helicobacter pylori* host-pathogen interactions: The triangle of virulence factors, epigenetic modifications and non-coding RNAs

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**Abstract**

*Helicobacter pylori* (*H. pylori*) is a model organism for understanding host-pathogen interactions and infection-mediated carcinogenesis. Gastric cancer and *H. pylori* colonization indicates the strong correlation. The progression and exacerbation of *H. pylori* infection are influenced by some factors of pathogen and host. Several virulence factors involved in the proper adherence and attenuation of immune defense to contribute the risk of emerging gastric cancer, therefore analysis of them is very important. *H. pylori* also modulates inflammatory and autophagy process to intensify its pathogenicity. From the host regard, different genetic factors particularly affect the development of gastric cancer. Indeed, epigenetic modifications, MicroRNA and long non-coding RNA received more attention. Generally, various factors related to pathogen and host that modulate gastric cancer development in response to *H. pylori* need more attention due to develop an efficacious therapeutic intervention. Therefore, this paper will present a brief overview of host-pathogen interaction especially emphases on bacterial virulence factors, interruption of host cellular signaling, the role of epigenetic modifications and non-coding RNAs.

**Key words:** Helicobacter pylori; Epigenetic; Virulence factor; Non-coding RNAs; Host pathogen interactions
virulence factors, interruption of host cellular signaling, the role of epigenetic modifications and non-coding RNAs.

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INTRODUCTION

Helicobacter pylori (H. pylori) introduced as a pathogen colonized the gastric mucosa for at least 58000 years. The longtime of co-evolution between H. pylori and host can indicate that its virulence decreased over time[14]. But, this bacterium involved in the development of chronic gastritis, peptic ulcer, gastric carcinoma, colorectal cancers, and MALT lymphoma that can cause the high burden of morbidity and mortality[2,3]. Epidemiological studies have indicated that the half of the world’s population is infected with this organism and more than 10%-15% of infected individuals develop severe gastric diseases[4,6]. Numerous studies indicated H. pylori as a strong cause of gastric cancer[6]. This rod-shaped Gram-negative microorganism has classified as a carcinogen group I by the International Agency for Research on Cancer (IARC)[7]. Gastric cancer, the third reason for mortality because of cancer after lung and liver cancer, is diagnosed in over 950000 patients and caused more than 720000 deaths every year[8]. The risk of H. pylori on gastric cancer is estimated almost 74%[9]. However, carcinogenesis develop in only a very small proportion of H. pylori colonized individuals and just 1%-3% develops gastric cancer[10]. The reason for various virulence level between different H. pylori strains are unknown, but it can partly be explained by several factors such as H. pylori virulence or the bacterial genotypes, geographical regions, host genetic traits, and environmental influences[11]. The investigations indicated more virulent strains have more associated with the development of gastric cancer[12]. Overall, the virulence factors, signaling pathways, and some host genetic traits received more attention. Clearly, the progression and exacerbation of H. pylori infection are influenced by some factors of pathogen and host. However, the precise mechanisms related to pathogen and host that modulate gastric cancer development in response to H. pylori need more attention. Therefore, this paper will present a brief overview of host-pathogen interaction especially associated with gastric cancer development in four parts: H. pylori virulence factors, interruption of host signaling, the role of epigenetic modifications and non-coding RNAs. The diagram of mentioned parts in association with gastric cancer presented in the Figure 1.

H. PYLORI VIRULENCE FACTORS ASSOCIATED WITH GASTRIC CANCER

Several virulence factor genes contribute the high heterogeneity of H. pylori[13]. Virulence factors increase the risk of emerging gastric carcinoma, therefore analysis of them in each region is very important[14]. H. pylori colonization in a niche near the surface of epithelial cells are known as the strongest but not sufficient risk factor, in this multi-factorial disease. The specific niche facilitates recognition of organisms by the immune system and H. pylori can modulate the inflammatory responses for its benefits[5]. Urease producing, motility and chemotaxis count as important properties of H. pylori to survive in the acidic environment of the stomach[12]. H. pylori able to produce a high level of urease into the stomach, which provides protection from gastric acidity. Urease produces NH3 and CO2 from urea and disrupts the epithelium by the production of ammonia. Ammonia interacts with neutrophil metabolites, induces the formation of carcinogenic agents and therefore increase the risk of gastric cancer. Besides, urease induces production of inflammatory cytokines[15]. Urease interacts with HLA class II molecules and CD74 on gastric cells. HLA class II molecules involved in regulation of immune responses and CD74 coordinate in antigen processing. Three genes code HLA class II molecules, HLA-DP, HLA-DQ, and HLA-DR, and more than 100 variant alleles have been detected. Some of these specific alleles are associated with gastric cancer[16]. Moreover, four to six polar flagella are essential for H. pylori motility[15]. In addition, H. pylori produces several effectors to intensify its pathogenicity. The CagA and specific alleles of VacA known as two best-studied virulence factors associated with the development of gastric cancer[11]. The CagA protein, encoded by the cytotoxin-associated genes (cag) pathogenicity island (PAI), carried by the most virulent H. pylori strains and the existence of cagA gene has a crucial role in the association of gastric cancer rates[17,18]. CagA introduced as the first bacterial oncoprotein. The type IV secretion system (T4SS) produced by the cagPAI and conveyed the CagA and some effector molecules like peptidoglycan into the cytoplasm of host’s gastric epithelial cells[19]. The imported CagA phosphorylated (and also remains un-phosphorylated) and initiates a signaling cascade that can perturb many host cell-signaling pathways and trigger pro-inflammatory responses, alteration of the cell polarity, disruption of the epithelial barrier and cytoskeletal rearrangements and cell elongation, induction of hummingbird phenotype, and promote the transformation of gastric epithelial cells[20]. Besides, CagA polymorphism is notable that may influence on severity of disease. The C-terminal of CagA contains specific repeated amino acids, including Glu-Pro-Ile-
Tyr-Ala, that known as EPIYA motif\(^ {21}\). The EPIYA motifs identified in 1993\(^ {22}\), including four different groups (named A, B, C, and D) based on the flanking amino acid arrangements and their position in CagA. The number and types of repeats in this region also influence on risk of carcinogenesis\(^ {23}\). Overall, this virulence factor is well studied and much of the related process well described. Western CagA and East Asian CagA strains known as two main genotypes of CagA that distinguished based on the structure of its EPIYA motif profiles. Western CagA strains usually have the EPIYA-A, EPIYA-B and EPIYA-C sequences in the EPIYA repeat region and East Asian CagA strains have just EPIYA-A and EPIYA-B without the EPIYA-C segment, but they have a specific EPIYA-D segment\(^ {24}\). Almost 70% and 90% of strains in some western and Asian countries presented the CagA virulence factor, respectively\(^ {25,26}\). Infections with positive CagA isolates have a high risk of severe disorders in comparison to infections with negative ones\(^ {27}\). Therefore, it can partly explain that why the highest incidence of gastric cancer reported from East Asia countries\(^ {28}\). All \textit{H. pylori} strains virtually produce a pore-forming protein, vacuolating cytotoxin (VacA) protein. The VacA uptakes by the host cells and forms vacuoles in the cytoplasm. The receptor protein tyrosine phosphatase (RPTP), RPTP-\(\alpha\) and RPTP-\(\beta\) as the cell surface receptors, play an important role in recognition and secretion of VacA\(^ {29}\). The function of VacA effectively depends on induction of membrane channel forming that influence on ion transport in the host cells, alteration in the cell membrane permeability, apoptosis, secretion of pro-inflammatory cytokines, modulation of immune cell function and induction of immunosuppressing\(^ {30}\). The various regions of VacA include the s-type (signal region), m-type (middle region), i-type (intermediate region), and d-type (deletion region)\(^ {31}\). The region of s, m, and i determine the formation of the channel, tropism to the host cells, and carcinogenic and vacuolating activity of VacA toxin, respectively. Deletion of 81 bp between the region of Figure 1 Diagram of main parts of \textit{Helicobacter pylori} host-pathogen interactions related to gastric carcinogenesis.
i and m known as d-type. Each of these regions subdivided. Allelic diversity influences the level of pathogenicity by the mosaic recombination between two major alleles of them (s1, s2, i1, i2, m1, m2). For instance, vacuolating strains have mostly vacA s1/m1 and vacA s1/m2 with i1 alleles. While non-vacuolating strains have vacA s2/m2 and vacA s1/m2 with i2 alleles. The vacA s1/m1 is strongly correlated with the development of gastric cancer. Actually, presence of strains with s1, m1, and i1 alleles are highly associated with the production of active toxins and gastric cancer. In addition, all s1 strains almost belong to positive CagA isolates and all s2/m2 strains belong to negative CagA isolates.

Other virulence factors produced by H. pylori, including BabA, SabA, OipA, NAP, Tipα, peptidoglycan, and LPS, are associated with the progression of infection. The blood-group antigen binding adhesion (BabA) and sialic acid binding protein A (SabA) count as two major outer membrane proteins (OMPs) that can serve as adhesion. BabA was found as a prominent adhesion of H. pylori. BabA binds to fucosylated glycoconjugates containing ABO/Lewis b blood group antigens on the gastric cells. SabA also is known as a key adhesion of H. pylori. BabA binds to specific components appeared in inflammation manner, a sialyl-Lewis x antigen on inflamed cells and MUC5B, which expressed only in a diseased manner. The attachment of this virulence factor increases survival chance of organism, helps to escape from sites with high bactericidal effects and increases accessibility to nutrients. Overall, the efficient binding of H. pylori in different conditions provides a proper situation for efficient delivery of effector molecules and modulation of host cells. Another major OMP in H. pylori are known as Outer inflammatory protein (OipA). According to Yamaoka’s research, OipA is associated with IL-8 levels. OipA induces secretion of IL-8 from gastric cells and plays a proinflammatory role in the H. pylori infection. OipA also involves in bacterial colonization. The neutrophil-activating protein (NAP) modulates the oxidative burst in neutrophils and induces inflammation during the H. pylori infection. Tipα (TNF-α inducing protein) is a novel effector related to carcinogenesis. Tipα ligates to a cell surface receptor encoded by NCL gene, nucleolin, and transfer to the nucleus. Nucleolin performs several functions in the nucleous, including RNA processing, chromatin remodeling, mRNA stabilization, DNA recombination, which may increase the risk of gastric cancer. In the nucleus of host cells, Tipα also binds to a different form of DNA and induces the expression of TNF-α and chemokines. In addition to proper adherence, attenuation of immune defense is a key step in the development of gastric cancer. The peptidoglycan and lipopolysaccharide (LPS), two the most important microbial associated molecular patterns (MAMPs) of H. pylori, ligate to pattern recognition receptors (PRRs). Thereby, H. pylori preserved from immune detection by various mechanisms such as phase variation, structural modification, molecular mimicry, and morphological transition that increased its persistence. Indeed, H. pylori virulence factors play a central role in the intensification of infection. Already, the impact of these virulence factors has been reviewed thoroughly.

**H. PYLORI INFECTION AND INTERRUPTION OF HOST SIGNALING**

In addition to virulence factors, H. pylori induces some modifications in host signaling cascades to intensify pathogenicity. In this regard, modulation of inflammatory and autophagy process are so interesting. H. pylori produces several inflammatory mediators, such as peptidoglycan, NAP, and LPS that increase the risk of oncogenesis. Environmental factors, including smoking, alcoholism, high intake of salt and low intake of fruits and vegetables can effect on activation of inflammatory signaling and secretion of cytokines and chemokines. Several PRRs recognize the MAMPs and damage associated molecular patterns (DAMP) that lead to the initiation of inflammatory responses. PRR generates signals to activate activator protein 1 (AP-1) and nuclear factor kappa-B (NF-κB) that finally produces related cytokines and chemokines. In addition, signaling of PRR leads to activation of some mechanisms for clearance of H. pylori. Furthermore, signaling of PRR plays both useful and harmful roles in hosts, clearance of pathogens and induction of carcinogenesis. Followed by the production of pro-inflammatory cytokines and chemokines, macrophages and granulocytes attract to the infection site and produce reactive nitrogen species (RNS) and reactive oxygen species (ROS). Moreover, H. pylori can directly induces production of ROS in gastric cells. These factors induce DNA damage and lead to oncogenic mutations. The inflammation initially caused by hypergastrinemia and destruction of D-cells. If inflammation persists, tissue damage because of gastrin level and hypochlorhydria occurs that can directly induce carcinogenic effects. Increasing gastrin level due to inflammation can directly heighten the risk of carcinogenesis. Gastrin binds to the cholecystokinin-2 receptor (CCK-2R), activates phosphoinositide3 kinase (PI3K)/Akt and JAK-STAT3 signaling pathways, and effect on adherence of host cells. Followed that can directly induce carcinogenic effects. In the autophagy process, cytoplasmic components are degraded in the lysosomes. In the autophagy process, ULK1 kinase complex (containing ULK1, ATG9 and the ATG2-WIPI1/2 complex function. The
vesicles assembly by the class III phosphatidylinositol 3-kinase complex[12,49]. Autophagy count as an essential process in function of antigen-presenting cells and activation of inflammatory responses[50]. Although autophagy has useful effects for the host, H. pylori can use some mechanisms to modulate it. VacA induces autophagy and this event can lead to interference of the autophagy process and production of defective autophagosome particles[51]. On the other hand, autophagy degrades the CagA[52]. Therefore, VacA help to CagA for the promotion of carcinogenesis by disruption in the autophagy[53]. Generally, autophagy plays a complex role in the carcinogenesis. Prolonged or forced autophagy formation increase the risk of host cell death and carcinogenesis[51].

**H. PYLORI INFECTION AND HOST TRAITS**

From the side of host, various significant changes create in H. pylori infection. Numerous studies indicated, different polymorphisms in the host genes have been associated with differing risk of gastric cancer[54,55]. This paper provides a brief of some host genetic factors that particularly affect the development of gastric cancer. Many of host factors related to the severity of H. pylori infection have been discussed elsewhere[54,56]. Indeed, epigenetic modifications, MicroRNA and long non-coding RNA, which has influence on the severity of H. pylori infection and gastric cancer development, will be discussed.

**EPIGENETIC MODIFICATIONS IN H. PYLORI INFECTION**

A growing area of interest is the investigation of epigenetic modifications in the pathogenicity of H. pylori. Epigenetic mechanisms regulate gene expression independent of direct modification of DNA sequence. Several types of epigenetic mechanisms are identified. First, methylation of DNA in cytosine or adenosine nucleotides by DNA methyltransferases. DNA methylation predominantly occurs on CpG islands and is associated with gene silencing. Second, histone modifications by phosphorylation, methylation, or acetylation regulate the accessibility of DNA to transcriptional factors and gene expression. Finally, chromatin remodeling and non-coding RNAs (ncRNA) which recently count as other major levels in epigenetic control; ncRNA is separately addressed in this review[57,58]. Modification of transcriptional profile of the host cells has been found as pathogen strategies to modulate host cells by various mechanisms to their benefits. Chronic exposure to H. pylori enhances DNA methylation and histone modifications particularly in the promoter region of tumor suppressor genes and oncogenes, that leads to silencing of them[57,59]. Induction of these epigenetic modifications by H. pylori is linked with oncogenesis and development of gastric cancer[60]. As mentioned, various types of cytokines, ROS, and RNS generate upon H. pylori infection that probably induces activation of DNA methyltransferases, may induce gene silencing[61]. Several studies have been published associating H. pylori infection with abnormally methylated genes in gastric cancer cases[62]. The more important of them include genes associated with cell growth, apc, p14(ARF), and p16(INK4a); the E-cadherin genes as cell adherence, cdh1, flnc, hand1, lox, hrasls, thbd, and p41ARC; genes associated DNA repair, braq1, mgmt, and hMLH1; and several other genes with unknown correlation with H. pylori infection[58,60,61,63]. For example, aberrant methylation in FOXD3, a fork head transcription factor with a tumor suppressor function, correlated with gastric cancer development. FOXD3 normally regulates transcription of proapoptotic factors. Therefore, hypermethylation of related promoter in gastric cancer inhibits activation FOXD3 and suppresses apoptosis[64]. Additional, GATA is known as a transcriptional family with six members that involved in host cells development. GATA2 is crucial for the development of hematopoietic cells whereas GATA6 is essential for the differential of gastrointestinal. Interestingly, hypermethylation of GATA2 repressed its expression while GATA6 overexpressed in gastric cancer cells[65]. Methylation-dependent silencing of the E-cadherin gene, a tumor suppressor gene, through IL-1β also known as main epigenetic changes in gastric cancer development. IL-1β stimulates NF-κB pathway that leads to activation of DNA methyltransferases and methylation of E-cadherin gene[66]. Besides, histone modifications and chromatin accessibility to transcription factors have been found significant in the progression of gastric cancer. Wide ranges of histone modifications that influence on tumor suppressor genes and oncogenes in response to H. pylori infection have been explored[58,67]. Modification in the phosphorylation status of H3 is associated with cell cycle arrest which induced by H. pylori. It can cause to inhibition of gastric cell renewal[68]. H. pylori also induces dephosphorylation of H3S10 and inhibits expression of NF-κB responsive genes[69]. Epigenetic change of the tumor suppressor protein p21 is linked with chronic H. pylori infection. Induction of histone acetylation of p21 gene by stimulation of a specific G-protein leads to the reduction of its expression in gastric cancer[67]. A study has shown that nuclease repositioning in CpG island p16 occurs in response to gastric cancer which induced by H. pylori. Nevertheless, interpretation of relevance of this data is difficult due to lack of more genome-wide investigations[70].

**MicroRNA and long non-coding RNA**

As mentioned, one of the most interesting fields in host-pathogen interaction is gene expression regulation, especially by RNA. RNA counted as a key regulatory
molecule and non-coding RNAs (ncRNA) recently added to the list of epigenetic regulators. Recognition by base-pairing allows one single ncRNA to bind multiple targets, and thereby to regulate several pathways simultaneously[71]. The ncRNA classified into two classes, microRNAs (miRNA) and long non-coding RNAs (IncRNA). The miRNA and IncRNA typically include 21-24 and more than 200 transcribed nucleotides by RNA polymerase II, respectively. To date, several distinct miRNA and IncRNA have been introduced that involved in gene expression regulation in different manners[72,73]. Some IncRNAs introduced which act in the response against bacterial infections. In bacterial infection, host cells employed miRNA and IncRNA to adjust gene expression program. Equally, pathogens employed various strategies, particularly by targeting ncRNAs, to overcome host defense mechanisms. Various pathogens activate expression of specific miRNAs in the host cells[74]. The bacteria manipulate the defense mechanisms of host cells by particularly modulating production of miRNA in order to increase pathogen survival. The main processes manipulated by down regulation or up regulation of various miRNAs including immune responses, autophagy, cell cycle and apoptosis[75]. The most important of these miRNAs include miR-146, miR-155, and let-7 family, which influence on immune responses in order to bacterial clearance[76]. The miR-146 and miR-155 are two main NF-κB-dependent miRNAs. The PRR activates NF-κB pathway by sensing of MAMPs and induced production of miR-155 and miR-146 that regulate distinct genes during infections[77,78]. The miR-146 counts as an anti-inflammatory regulator and targets IRAK1 (IL-1R-associated kinase 1) and TRAF6 (TNF Receptor-associated factor 6) in the NF-κB pathway that increases tolerance to a low dose of LPS[79]. The role of miR-146 is also crucial for intestinal microbiota due to the prevention of inappropriate inflammation[79]. The miR-155 induces expression of pro-inflammatory cytokines, including TNF-α, IL-6, IL-1β, IL-8, and IL-12, and acts as an essential factor against infections[39,78]. Besides, miR-155 involved in the development of T helper cells and autophagy by suppressing the mTOR pathway[80]. This miRNA represses some genes, NIK, IKKε, and TAB; encoding proteins involved in the inflammatory pathway and limits the inflammation. Interestingly, NOD2 receptor stimulated the expression of miR-155. Generally, miR-155 acts as a negative regulator to adjust inflammatory responses in H. pylori infection[75]. Another miRNA, which targets various genes in immunity, is let-7. Upon infections, let-7 repressed by activation of NF-κB pathway because of exposure to LPS[70]. The NF-κB pathway induces expression of Lin-28B, which inhibit maturation of let-7. In addition, some bacteria directly repress this miRNA[81,82].

H. pylori induces expression of miR-30b, which influences on the transcript of proteins that involved in the formation of autophagosomes and so its effects on autophagy process[83]. In the following, up regulation or down regulation of specific miRNAs involved in different steps of cell cycle described. Overexpression of miR-21 and miR-222 that target RECK, a tumor suppressor, induce proliferation of gastric cells[84,85]. CagA induces the expression of miR-584 and miR-1290 that influence on epithelial-mesenchymal transition by targeting of FOXA1, a related negative regulator[86]. In addition, down regulation of miR-320 and miR-370 in a CagA dependent manner also noticed in H. pylori infections. The miR-320 induces expression of MCL1, an anti-apoptotic gene. The miR-370 down regulates expression of FoxM1 and subsequently activates p27kip1, a cell cycle inhibitor. Therefore, down regulation of miR-320 and miR-370 can lead to tumor suppression through decreasing apoptosis and increasing cell proliferation[87,88]. CagA of H. pylori activates NF-κB pathway and downregulates expression of miR-372 and miR-373, which inhibit renewal of gastric epithelium by blocking of cell cycle progression in the G1-S checkpoint[89]. H. pylori also induces expression of miR-1289 in a CagA dependent manner, which finally decrease gastric acidity and increase the possibility of H. pylori colonization[90]. These data suggested a link between H. pylori infection and gastric cancer development.

Most investigations focused on the role of IncRNAs in host-pathogen interaction on viral infections, but its role in inflammatory responses has recently elucidated. The regulatory IncRNAs participate in almost every part of gene expression and can interact with DNA, RNA, and protein. Therefore, disruption in the expression of IncRNAs and subsequently alteration of cellular pathways have been discovered in gastric cancer studies[91]. In the following, briefly described some of the most important oncogenic IncRNAs involved in cell proliferation, apoptosis, and metastasis processes in gastric cancer. For instance, the aberrant expression GAPLINC (gastric adenocarcinoma predictive long intergenic noncoding RNA) markedly correlated with alteration of CD44 and thereby increased proliferation and angiogenesis of cancer cells. GAPLINC is known as a decoy molecule to protect CD44 from degradation[92]. Uregulation of HOTAIR, ANRIL, and GHT1 has been found in gastric cancer. This upregulation directly related to cell proliferation, invasion, and progression of cancer[93-95]. The IncRNA H19 overexpressed in gastric cancer. The production of miR-675 related to H19 that directly silences certain tumor suppressor, RUNX1, and increases cell proliferation and inhibits apoptosis[96]. H19 directly inhibit the function of p53, a tumor suppressor molecule, and leading to cell proliferation[97]. CCAT1 overexpressed in gastric cancer and promoted cell proliferation[98]. Overexpression of MALAT1 induced localization of SF2/ASF proteins in the nucleus that involved in splicing. Therefore, MALAT1 may partly modulate cell proliferation by regulation of SF2/ASF expression[99]. Overexpression of HULC well described in hepatocellular carcinoma, but the high level of it also shown in gastric cancer and related to proliferation[100].
Downregulation of *FENDRR* (FOXF1 adjacent non-coding developmental regulatory RNA) is associated with cell invasion and migration in gastric cancer\(^{101}\). Downregulation of *GASS* (growth arrest-specific transcript 5) plays an important role in the proliferation of gastric cells. *GASS* interacts with YBX1, a transcriptional activator, and subsequently induces expression of p21. Therefore, downregulation of *GASS* eventually leads to abolishing of cell cycle arrest\(^{101}\). Downregulation of *MEG3* (maternally expressed gene 3) is correlated with cell proliferation and inhibition of apoptosis in gastric cancer cells\(^{102}\). Downregulation of *LincBM742401* has been closely associated with cell metastasis\(^{103}\). To achieve better understanding of the importance of IncRNAs in *H. pylori* infection more investigations are inevitable\(^{104,105}\). In fact, accumulating data indicate participation and collaboration of miRNAs and IncRNAs to modulate gene expression and gastric cancer development.

### FEATURE PERSPECTIVE

In summary, nowadays, the knowledge of factors involved in *H. pylori* disease pathogenesis can be elucidated and refined. We tried to review salient host and pathogen factors that influence on gastric cancer in *H. pylori* infection. Ultimately, the development of efficacious therapeutic interventions will likely need to switch host-pathogen interactions science to translational research for enhancing host immunity and circumvent bacterial evasion strategies.

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### REFERENCES

1. Amieva M, Peek RM Jr. Pathobiology of Helicobacter pylori-Induced Gastric Cancer. *Gastroenterology* 2016; 150: 64-78 [PMID: 26385073 DOI: 10.1053.j.gastro.2015.09.004]
2. Miftahussurur M, Yamaoka Y, Graham DY. Helicobacter pylori as an oncogenic pathogen, revisited. *Expert Rev Mol Med* 2017; 19: e8 [PMID: 28322182 DOI: 10.1017/erm.2017.4]
3. Engin AB, Karahalil B, Karakaya AE, Engin A. Helicobacter pylori and serum kynurenine-tryptophan ratio in patients with colorectal cancer. *World J Gastroenterol* 2015; 21: 3636-3643 [PMID: 25834331 DOI: 10.3748/wjg.v21.i22.3636]
4. Pachathundikadki SK, Lind J, Tegtmeier N, El-Omar EM, Backert S. Interplay of the Gastric Pathogen Helicobacter pylori with Toll-Like Receptors. *Biomed Res Int* 2015; 2015: 192420 [PMID: 25945326 DOI: 10.1155/2015/192420]
5. Lind J, Backert S, Hoffmann R, Eichel J, Yamaoka Y, Perez-Perez GI, Torres J, Sticht H, Tegtmeier N. Systematic analysis of phosphotyrosine antibodies recognizing single phosphorylated EPIYA-motifs in CagA of East Asian-type Helicobacter pylori strains. *BMC Microbiol* 2016; 16: 201 [PMID: 27590005 DOI: 10.1186/s12866-016-0820-6]
6. Cover TL. Helicobacter pylori Diversity and Gastric Cancer Risk. *MBio* 2016; 7: e01869-e01815 [PMID: 26814181 DOI: 10.1128/mBio.01869-15]
7. Schistoosomes, liver flukes and Helicobacter pylori. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7-14 June 1994. *IARC Monogr Eval Carcinog Risks Hum* 1994; 61: 1-241 [PMID: 7719689]
8. Stewart B, Wild CP. World Cancer report 2014, Health, 2017
9. Parkin DM. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer* 2006; 118: 3030-3044 [PMID: 16404738 DOI: 10.1002/ijc.21731]
10. Giorgio A, Iacoviello G, D’Avino A. Biology of the “Salmonella wien” (author’s transl). *Ann Scelvo* 1976; 18: 563-573 [PMID: 1020968]
11. Li Q, Liu J, Gong Y, Yuan Y. Association of CagA EPIYA-D or EPIYA-C phosphorylation sites with peptic ulcer and gastric cancer risks: A meta-analysis. *Medicine* (Baltimore) 2017; 96: e6620 [PMID: 28445260 DOI: 10.1097/MD.0000000000006620]
12. Mommersteeg MC, Yu J, Peppelenbosch MP, Fuhler GM. Genetic host factors in Helicobacter pylori-induced carcinogenesis: Emerging new paradigms. *Biochim Biophys Acta* 2018; 1869: 42-52 [PMID: 29154808 DOI: 10.1016/j.bbcan.2017.11.003]
13. Bagheri N, Azadeh-Dekordi F, Rafieian-Kopaei M, Rahimian G, Asadi-Samani M, Shirzad H. Clinical relevance of Helicobacter pylori virulence factors in Iranian patients with gastrointestinal diseases. *Microb Pathog* 2016; 100: 154-162 [PMID: 27666510 DOI: 10.1016/j.micpath.2016.09.016]
14. Vaziri F, Najar Peerayeh SN, Alebouyeh M, Mirzaei T, Yamaoka Y, Molaei M, Maghsoudi N, Zali MR. Diversity of Helicobacter pylori genotypes in Iranian patients with different gastroduodenal disorders. *World J Gastroenterol* 2013; 19: 5685-5692 [PMID: 24039362 DOI: 10.3748/wjg.v19.i24.5685]
15. Roessler BM, Rabelo-Goncalves EM, Zeitme IM. Virulence Factors of Helicobacter pylori: A Review. *Clin Med Insights Gas Insights Gastroenterol* 2014; 7: 9-17 [PMID: 24833944 DOI: 10.4137/Cmgas.S13760]
16. He C, Chen M, Liu J, Yuan Y. Host genetic factors respond to pathogenic step-specific virulence factors of Helicobacter pylori in gastric carcinogenesis. *Mutat Res Rev Mutat Res* 2014; 759: 14-26 [PMID: 24076409 DOI: 10.1016/j.mrrev.2013.09.002]
17. Yamaoka Y, Kodanana T, Kashima K, Graham DY, Sepulveda AR. Variants of the 3’ region of the cag A gene in Helicobacter pylori isolates from patients with different H. pylori-associated diseases. *J Clin Microbiol* 1998; 36: 2258-2263 [PMID: 9666002]
18. Vaziri F, Peerayeh SN, Alebouyeh M, Maghsoudi N, Azimzadeh P, Siadat SD, Zali MR. Novel effects of Helicobacter pylori CagA on key genes of gastric cancer signal transduction: a comparative transfection study. *Pathog Dis* 2015; 73 [PMID: 25743471 DOI: 10.1093/femspd/ftu021]
19. Hatakeyama M. Structure and function of Helicobacter pylori CagA, the first-identified bacterial protein involved in human cancer. *Proc Jpn Acad Ser B Phys Biol Sci* 2017; 93: 196-219 [PMID: 28413197 DOI: 10.2183/pjab.93.013]
20. Backert S, Tegtmeier N, Selbach M. The versatility of Helicobacter pylori CagA effector protein functions: The master key hypothesis. *Helicobacter* 2010; 15: 163-176 [PMID: 20557357 DOI: 10.1111/j.1523-5378.2010.00759.x]
21. Vaziri F, Peerayeh SN, Alebouyeh M, Maghsoudi N, Azimzadeh P, Siadat SD, Zali MR. Determination of Helicobacter pylori CagA protein expression in gastric cancers in the year 2002. *Int J Cancer* 2003; 101: 1869-1876 [PMID: 12850774 DOI: 10.1002/ijc.11354]
22. Covacci A, Censis S, Bugnoli M, Petracca R, Burroni D, Macchia G, Massone A, Papini E, Xiang Z, Figura N. Molecular characterization of the 128-kDa immunodominant antigen of Helicobacter pylori associated with cytotoxicity and duodenal ulcer. *Proc Natl Acad Sci USA* 1993; 90: 5791-5795 [PMID: 8516329]
23. Vaziri F, Najar Peerayeh SN, Alebouyeh M, Molaei M, Maghsoudi N, Zali MR. Determination of Helicobacter pylori CagA EPIYA types in Iranian isolates with different gastroduodenal disorders. * Infect Genet Evol* 2013; 17: 101-105 [PMID: 23567822 DOI: 10.1016/j.meegid.2013.03.048]
24. Vianna JS, Ramis IB, Halicki PC, Gastal OL, Silva RA, Junior JS, Dos Santos DM, Chaves AL, Juliano CR, Jannke HA, da Silva LV Jr, Von Groll A, da Silva PE. Detection of Helicobacter pylori CagA EPIYA in gastric biopsy specimens and its relation to gastric diseases. *Diagn Microbiol Infect Dis* 2015; 83: 89-92 [PMID: 26144892 DOI: 10.1016/j.diagmicrobio.2015.05.017]
The intriguing relationship of Helicobacter pylori and innate immunity in gastric carcinoma: Results from a Human C. jejune CagA Phosphorylation Site Study. *J Gastrointest Liver Dis* 2017; 26: 135-140 [PMID: 28453555 DOI: 10.1017/jjgl.2016.252]

Kawanishi S, Onishi S, Ma N, Hiraku Y, Oikawa S, Murata M. Nitrative and oxidative DNA damage in infection-related carcinogenesis in relation to cancer stem cells. *Genes Environ* 2017; 38: 26 [PMID: 28050219 DOI: 10.1186/s41021-016-0055-7]

Malfertheiner P. The intriguing relationship of Helicobacter pylori infection and acid secretion in peptic ulcer disease and gastric cancer. *Dig Dis* 2011; 29: 459-464 [PMID: 22095010 DOI: 10.1159/000332213]

Smith JP, Nadelia S, Osborne N. Gastrin and Gastric Cancer. *Cell Mol Gastroenterol Hepatol* 2017; 4: 75-83 [PMID: 28560291 DOI: 10.1016/j.cgh.2017.03.004]

Roy J, Puth KS, Coppola D, Leon ME, Khalil FK, Centeno BA, Clark N, Stark VE, Morse DL, Low PS. Assessment of cholecystokinin 2 receptor (CCK2R) in neoplastic tissue. *Oncotarget* 2016; 7: 14605-14615 [PMID: 26910279 DOI: 10.18632/oncotarget.7522]

Koh TJ, Chen D. Gastrin as a growth factor in the gastrointestinal tract. *Regul Pept* 2000; 93: 37-44 [PMID: 11303051]

Mizushima N. Autophagy: process and function. *Genes Dev* 2007; 21: 2861-2873 [PMID: 18006683 DOI: 10.1101/gad.1599207]

Chauhan S, Mandell MA, Deretic V. IRGM governs the core autophagy machinery to conduct antimicrobial defense. *Mol Cell* 2015; 58: 507-521 [PMID: 25891078 DOI: 10.1016/j.molcel.2015.03.020]

Shibutani ST, Saitoh T, Nowag H, Münz C, Yoshimori T. Autophagy and autophagy-related proteins in the immune system. *Nat Immunol* 2015; 16: 1014-1024 [PMID: 26382870 DOI: 10.1038/ni.3273]

Terebiznik MR, Raju D, Vázquez CL, Torbricki K, Kalkarni R, Blanke SR, Yoshimori T, Colombo MI, Jones NL. Effect of Helicobacter pylori’s vacuolating cytotoxin on the autophagy pathway in gastric epithelial cells. *Autophagy* 2009; 5: 370-379 [PMID: 19164948]

Jones KR, Whitmire JD, Merrell DS. A Tale of Two Toxins: Helicobacter Pylori CagA and VacA Modulate Host Pathways that Impact Disease. *Front Microbiol* 2010; 1: 115 [PMID: 21687723 DOI: 10.3389/fmicb.2010.00115]

Júnior MF, Batista SA, Barbuto RC, Gomes AD, Queiroz DM, Araújo ID, Caliari MV. CagA-positive Helicobacter pylori strain containing three EPIYA C phosphorylation sites produces increase in gastric carcinogenesis in relation to cancer stem cells. *Aliment Pharmacol Ther* 2017; 45: 1067-1079 [PMID: 28453555 DOI: 10.1111/apt.14345]

Ma J, Wu D, Hu X, Li J, Cao M, Dong W. Associations between cytokine gene polymorphisms and susceptibility to Helicobacter pylori infection and Helicobacter pylori related gastric cancer, peptic ulcer disease: A meta-analysis. *PLoS One* 2017; 12: e0176463 [PMID: 28453555 DOI: 10.1371/journal.pone.0176463]

Melchjies JL, Zabaglia LM, Sallas ML, Orcini WA, Chen E, Smith MAC, Payán SL, Rasmussen LT. Polymorphisms and haplotypes of the interleukin 2 gene are associated with an increased risk of gastric cancer. The possible involvement of Helicobacter pylori virulence factors. *Nat Rev Gastroenterol Hepatol* 2010; 7: 629-641 [PMID: 20938460 DOI: 10.1038/nrgastro.2010.154]

Fiskell C, Wilson KT. Role of innate immunity in gastric mucosal cells. *Am J Physiol Cell Physiol* 2005; 288: C450-C457 [PMID: 15446995 DOI: 10.1152/ajpcell.00319.2004]

Kawanishi S, Onishi S, Ma N, Hiraku Y, Oikawa S, Murata M. Nitrative and oxidative DNA damage in infection-related carcinogenesis in relation to cancer stem cells. *Genes Environ* 2017; 38: 26 [PMID: 28050219 DOI: 10.1186/s41021-016-0055-7]

Malfertheiner P. The intriguing relationship of Helicobacter pylori infection and acid secretion in peptic ulcer disease and gastric cancer. *Dig Dis* 2011; 29: 459-464 [PMID: 22095010 DOI: 10.1159/000332213]

Smith JP, Nadelia S, Osborne N. Gastrin and Gastric Cancer. *Cell Mol Gastroenterol Hepatol* 2017; 4: 75-83 [PMID: 28560291 DOI: 10.1016/j.cgh.2017.03.004]
Vaziri F et al. Helicobacter pylori host-pathogen interactions

59  Gorrell R, Kwok T. The Helicobacter pylori Methylome: Roles in Gene Regulation and Virulence. Curr Top Microbiol Immunol 2017; 400: 105-127 [PMID: 28124515 DOI: 10.1007/978-3-319-50250-6_5]

60  Sitarraman R. Helicobacter pylori DNA methyltransferases and the epigenetic field effect in carcinogenesis. Front Microbiol 2014; 5: 115 [PMID: 24723914 DOI: 10.3389/fmicb.2014.00115]

61  Nardone G, Compare D, De Colibus P, deucci G, Rocco A. Helicobacter pylori and epigenetic mechanisms underlying gastric carcinogenesis. Dig Dis 2007; 25: 225-229 [PMID: 17827945 DOI: 10.1159/000103890]

62  Santos JC, Ribeiro ML. Epigenetic regulation of DNA repair machinery in Helicobacter pylori-induced gastric carcinogenesis. World J Gastroenterol 2015; 21: 9021-9037 [PMID: 26290630 DOI: 10.3748/wjg.v21.i30.9201]

63  Maekita T, Nakazawa K, Mihara M, Nakajima T, Yanoaka K, Iguchi M, Arii K, Kaneda A, Tsukamoto T, Tatematsu M, Tamura G, Saito D, Sugimura T, Ichinose M, Ushijima T. High levels of aberrant DNA methylation in Helicobacter pylori-infected gastric mucosa and its possible association with gastric cancer risk. Clin Cancer Res 2006; 12: 899-905 [PMID: 16467114 DOI: 10.1186/1078-0432.CCR-05-2096]

64  Cheng AS, Li MS, Kang W, Cheng YV, Chou JL, Lau SS, Go MY, Lee CC, Ling TK, Ng EK, Yu J, Huang TH, To FK, Chan MW, Sun JJ, Chan FK. Helicobacter pylori causes epigenetic dysregulation of FOXP3 to promote gastric carcinogenesis. Gastroenterology 2013; 144: 122-133.e9 [PMID: 23058321 DOI: 10.1053/j.gastro.2012.10.002]

65  Song SH, Jeon MS, Nam JW, Kang JK, Lee VJ, Kang YJ, Kim HP, Han SW, Kang GH, Kim TY. Ablerrant GATA2 epigenetic dysregulation induces a GATA2/GATA6 switch in human gastric cancer. Oncogene 2018; 37: 993-1004 [PMID: 29106391 DOI: 10.1038/onc.2017.397]

66  Huang FY, Chan AO, Rashid A, Wong DK, Cho CH, Yuen MF. Helicobacter pylori induces promoter methylation of E-cadherin via inter leukin-1β activation of nitric oxide production in gastric cancer cells. Cancer Lett 2012; 326: 96-104 [PMID: 22867947 DOI: 10.1016/j.canlet.2012.07.032]

67  Fehri LF, Rechner C, Janssen M, Mak TN, Holland C, Bartfeld F, Brüggemann H, Meyer TF. Helicobacter pylori-induced promoter methylation of E-cadherin correlates with reduced E-cadherin expression in human gastric cancer cells. Lab Invest 2012; 92: 105-127 [PMID: 22321642 DOI: 10.1038/151030]

68  Ding SZ, Fischer W, Kaparakis-Liaskos M, Liechti G, Merrell DS, Grant PA, Ferrero RL, Crowe SE, Haas R, Hatakeyama M. Helicobacter pylori-induced histone modification, associated gene expression in gastric epithelial cells, and its implication in pathogenesis. PLoS One 2010; 5: e9875 [PMID: 20368982 DOI: 10.1371/journal.pone.0009875]

69  Lu ZM, Zhu J, Wang X, Guan Z, Bai H, Liu ZJ, Su N, Pan K, Ji D, Jeng D. Nucleosomes correlate with in vivo progression pattern of de novo methylation of p16 Cpg islands in human gastric carcinogenesis. PLoS One 2012; 7: e35928 [PMID: 22558275 DOI: 10.1371/journal.pone.0035928]

70  Peterson SM, Thompson JA, Uffink ML, Sathyanarayana P, Liaw L, Congdon CB. Common features of microRNA target prediction tools. Front Genet 2014; 5: 23 [PMID: 24600468 DOI: 10.3389/fgene.2014.00023]

71  Quan M, Chen J, Zhang D. Exploring the secrets of long noncoding RNAs. Int J Mol Sci 2015; 16: 5467-5496 [PMID: 25764159 DOI: 10.3390/ijms16053467]

72  Friedman RC, Farh KK, Burge CB, Bartel DP. Most mammalian mRNAs are conserved targets of microRNAs. Genome Res 2009; 19: 92-105 [PMID: 18955434 DOI: 10.1101/gr.082701.108]

73  Jin W, Beagha-Awemu EM, Liang G, Beaudoin F, Xiao S, Zhang D. Exploring the secrets of long noncoding RNAs. Int J Mol Sci 2015; 16: 5467-5496 [PMID: 25764159 DOI: 10.3390/ijms16053467]
antiapoptotic protein Mcl-1. *Am J Physiol Gastrointest Liver Physiol* 2013; **305**: G786-G796 [PMID: 24136787 DOI: 10.1152/ajpgi.00279.2013]

99 Belair C, Baud J, Chabas S, Sharma CM, Vogel J, Staedel C, Darfeuille F. Helicobacter pylori interferes with an embryonic stem cell micro RNA cluster to block cell cycle progression. *Silence* 2011; **2**: 7 [PMID: 22027184 DOI: 10.1186/1757-907X-2-7]

100 Zhang YM, Noto JM, Hammond CE, Barth JL, Argraves WS, Baud J, Chabas S, Sharma CM, Vogel J, Staedel C, Zhuang M. Long non-coding RNA H19 contributes to proliferation of gastric cancer cells. *FEBS J* 2012; **279**: 3159-3165 [PMID: 22776265 DOI: 10.1111/j.1742-4658.2012.08694.x]

101 Yang F, Xue X, Bi J, Zheng L, Zhi K, Gu Y, Fang G. Long noncoding RNA CCAT1, which could be activated by c-Myc, promotes the progression of gastric carcinoma. *J Cancer Res Clin Oncol* 2013; **139**: 437-445 [PMID: 23143645 DOI: 10.1007/s00432-012-1324-x]

102 Wang J, Su L, Chen X, Li P, Cai Q, Yu B, Liu B, Wu W, Zhu Z. MALAT1 promotes cell proliferation in gastric cancer by recruiting SF2/ASF. *Biomed Pharmacother* 2014; **68**: 557-564 [PMID: 24857172 DOI: 10.1016/j.biopha.2014.04.007]

103 Zhao Y, Guo Q, Chen J, Hu J, Wang S, Sun Y. Role of long non-coding RNA HULC in cell proliferation, apoptosis and tumor metastasis of gastric cancer: a clinical and in vitro investigation. *Oncol Rep* 2014; **31**: 358-364 [PMID: 24247585 DOI: 10.3892/or.2013.2850]

104 Hu Y, Wang J, Qian J, Kong X, Tang J, Wang Y, Chen H, Hong J, Zou W, Chen Y, Xu J, Fang JY. Long noncoding RNA GAPLINC regulates CD44-dependent cell invasiveness and associates with poor prognosis of gastric cancer. *Cancer Res* 2014; **74**: 6890-6902 [PMID: 25277524 DOI: 10.1158/0008-5472.CAN-14-0686]

105 Lee NK, Lee JH, Park CH, Yu D, Lee YC, Cheong JH, Noh SH, Lee SK. Long non-coding RNA HOTAIR promotes carcinogenesis and invasion of gastric adenocarcinoma. *Biochem Biophys Res Commun* 2014; **451**: 171-178 [PMID: 25063030 DOI: 10.1016/j.bbrc.2014.07.067]

106 Zhang EB, Kong R, Yin DD, You LH, Sun M, Han L, Xu TP, Xia R, Yang JS, De W, Shu YQ. Decreased expression of the long non-coding RNA FENDRR is associated with poor prognosis in gastric cancer and FENDRR regulates gastric cancer cell metastasis by affecting fibronectin1 expression. *J Hematol Oncol* 2014; **7**: 63 [PMID: 25167886 DOI: 10.1186/s13045-014-0063-7]

107 Sun M, Xia R, Jin F, Xu T, Liu Z, De W, Liu X. Downregulated long noncoding RNA MEG3 is associated with poor prognosis and promotes cell proliferation in gastric cancer. *Tumour Biol* 2014; **35**: 1065-1073 [PMID: 24066224 DOI: 10.1007/s13277-013-1142-z]

108 Park SM, Park SJ, Kim HJ, Kwon OH, Kang TW, Sohn HA, Kim SK, Moe Noh S, Song KS, Jung SJ, Sung Kim Y, Kim SY. A known expressed sequence tag, BM742401, is a potent long RNA inhibiting cancer metastasis. *Exp Mol Med* 2013; **45**: e31 [PMID: 23846333 DOI: 10.1038/emm.2013.39]

109 Zhou X, Chen H, Zhu L, Hao B, Zhang W, Hua J, Gu H, Jin W, Zhang G. Helicobacter pylori infection related long noncoding RNA (IncRNA) AF147447 inhibits gastric cancer proliferation and invasion by targeting MUC2 and up-regulating miR-34c. *Exp Mol Med* 2013; **45**: e31 [PMID: 23846333 DOI: 10.1038/emm.2013.39]

110 Zhou X, Chen H, Zhu L, Hao B, Zhang W, Hua J, Gu H, Jin W, Zhang G. Helicobacter pylori infection related long noncoding RNA (IncRNA) AF147447 inhibits gastric cancer proliferation and invasion by targeting MUC2 and up-regulating miR-34c. *Exp Mol Med* 2013; **45**: e31 [PMID: 23846333 DOI: 10.1038/emm.2013.39]

111 Zhu H, Wang Q, Yao Y, Fang J, Sun F, Ni Y, Shen Y, Wang H, Shao S. Microarray analysis of Long non-coding RNA expression profiles in human gastric cells and tissues with Helicobacter pylori Infection. *BMC Med Genomics* 2015; **8**: 84 [PMID: 26690385 DOI: 10.1186/s12920-015-0159-0]
