ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2018 May 16; 6(5): 64-98

Published by Baishideng Publishing Group Inc

WJCC

World Journal of Clinical Cases

Contents

Monthly Volume 6 Number 5 May 16, 2018

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World Journal of Clinical Cases
Volume 6 Number 5 May 16, 2018

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INDEXING/ABSTRACTING

World Journal of Clinical Cases is now indexed in PubMed, PubMed Central, Science Citation Index Expanded (also known as SciSearch®), and Journal Citation Reports/Science Edition.

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NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Monthly

EDITORIAL OFFICE
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World Journal of Clinical Cases
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7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
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E-mail: editorialoffice@wjgnet.com
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7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
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PUBLICATION DATE
May 16, 2018

INSTRUCTIONS TO AUTHORS
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World Journal of Clinical Cases

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World J Clin Cases 2018 May 16; 6(5): 64-73

DOI: 10.12998/wjcc.v6.i5.64

ISSN 2307-8960 (online)

REVIEW

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

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Author contributions: All authors contributed to the manuscript.

Conflict-of-interest statement: No potential conflicts of interest relevant to this article were reported.

Manuscript source: Invited manuscript

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Received: January 14, 2018
Peer-review started: January 15, 2018
First decision: January 22, 2018
Revised: February 9, 2018
Accepted: March 7, 2018
Article in press: March 7, 2018
Published online: May 16, 2018

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

Core tip: As *Helicobacter pylori* (*H. pylori*) is a model organism for understanding host-pathogen interactions and infection-mediated carcinogenesis, ongoing studies in this area should have broad relevance to these conditions. In this context, we tried to review salient host and pathogen factors that influence on gastric cancer in *H. pylori* infection with emphasis on bacterial

virulence factors, interruption of host cellular signaling, the role of epigenetic modifications and non-coding RNAs.

Vaziri F, Tarashi S, Fateh A, Siadat SD. New insights of *Helicobacter pylori* host-pathogen interactions: The triangle of virulence factors, epigenetic modifications and non-coding RNAs. *World J Clin Cases* 2018; 6(5): 64-73 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i5/64.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i5.64

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[1]. 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[4,5]. 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[1]. 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-

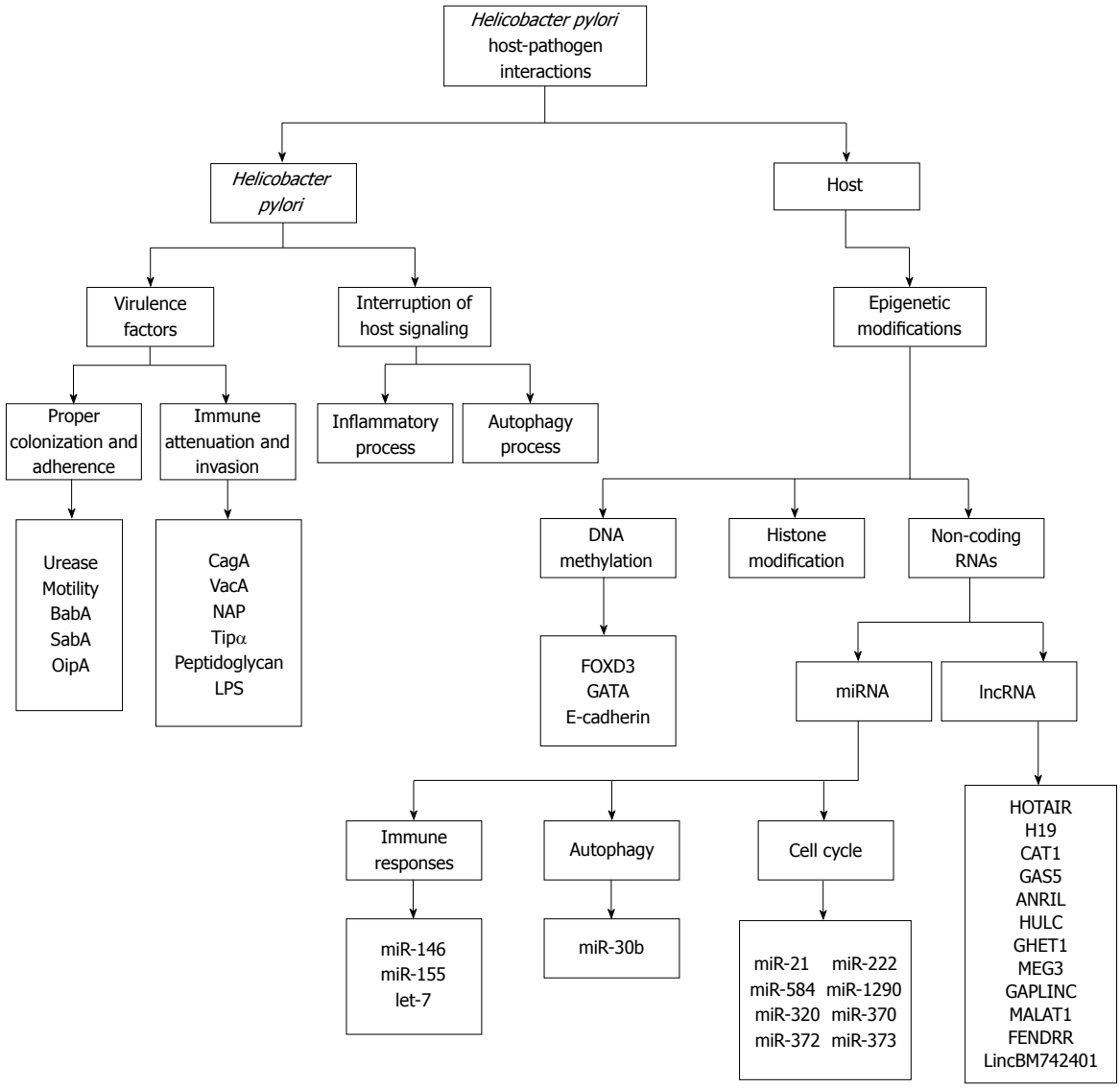

Figure 1 Diagram of main parts of *Helicobacter pylori* host-pathogen interactions related to gastric carcinogenesis.

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 *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-α and RPTP-β 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

i and m known as d-type[32]. 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[15]. 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[28,33]. In addition, all s1 strains almost belong to positive CagA isolates and all s2/m2 strains belong to negative CagA isolates[34].

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*. SabA 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[35]. 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[16]. 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[36]. OipA induces secretion of IL-8 from gastric cells and plays a proinflammatory role in *H. pylori* infection[15]. OipA also involves in bacterial colonization[37]. The neutrophil-activating protein (NAP) modulates the oxidative burst in neutrophils and induces inflammation during the *H. pylori* infection[15]. 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 rRNA processing, chromatin remodeling, mRNA stabilization, DNA recombination, which may increase the risk of gastric cancer[38]. In the nucleus of host cells, Tipα also binds to a different form of DNA and induces the expression of TNF-α and chemokines[16]. 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[39]. 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[28,40,41].

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[12]. 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[12]. 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[42]. These factors induce DNA damage and lead to oncogenic mutations[43]. The inflammation initially caused by hypergastrinemia and destruction of D-cells. If inflammation persists, tissue damage because of gastrin level and hypochlorhydria occurs[44] 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[45]. CCK-2R upregulates in different types of cancers[46]. This event cause loss of acid producing cells and deregulates expression of some growth factors that influence on cell differentiation[47]. This deregulation may influence on the development of carcinogenesis[12].

In addition, autophagy as a self-degrading mechanism counts significant in *H. pylori* pathogenicity. In autophagy process, cytoplasmic components are degraded in the lysosomes[48]. In the autophagy process, ULK1 kinase complex (containing ULK1-mAtg13, FIP200, and ATG101) formed by induction of IRGM to form autophagy. Then, autophagosome formed by 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[41,56]. 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, *brca1*, *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 p27 is linked with chronic *H. pylori* infection. Induction of histone acetylation of *p27* gene by stimulation of a specific G-protein leads to the reduction of its expression in gastric cancer[67]. A study has shown that nucleosome 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 (lncRNA). The miRNA and lncRNA typically include 21-24 and more than 200 transcribed nucleotides by RNA polymerase Ⅱ, respectively. To date, several distinct miRNA and lncRNA have been introduced that involved in gene expression regulation in different manners[72,73]. Some lncRNAs introduced which act in the response against bacterial infections. In bacterial infection, host cells employed miRNA and lncRNA 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[78]. 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[76]. 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 $p27^{KIP1}$, 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 lncRNAs in host-pathogen interaction on viral infections, but its role in inflammatory responses has recently elucidated. The regulatory lncRNAs participate in almost every part of gene expression and can interact with DNA, RNA, and protein. Therefore, disruption in the expression of lncRNAs 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 lncRNAs 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]. Upregulation of HOTAIR, ANRIL, and GHET1 has been found in gastric cancer. This upregulation directly related to cell proliferation, invasion, and progression of cancer[93-95]. The lncRNA *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 *GAS5* (growth arrest-specific transcript 5) plays an important role in the proliferation of gastric cells. *GAS5* interacts with YBX1, a transcriptional activator, and subsequently induces expression of *p21*. Therefore, downregulation of *GAS5* eventually leads to abolishing of cell cycle arrest[91]. 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 lncRNAs in *H. pylori* infection more investigations are inevitable[104,105]. In fact, accumulating data indicate participation and collaboration of miRNAs and lncRNAs to modulate gene expression and gastric cancer development.

FEATURE PERSPECTIVE

In summary, nowadays, the knowledge of factors involved in *H. pylori* disease pathogenesis continues to 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.

ACKNOWLEDGMENTS

We tender our apologies to those authors whose deserving research was not cited in this manuscript.

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P- Reviewer: Bernal G, Bugaj AM, Buzas GM, Dinc T, Engin AB, Niu ZS, Paoluzi OA, Zhu YL **S- Editor**: Cui LJ
L- Editor: A **E- Editor**: Wang CH

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