ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2017 June 14; 23(22): 3945-4134

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents

Weekly Volume 23 Number 22 June 14, 2017

EDITORIAL

REVIEW

ORIGINAL ARTICLE

Basic Study

Case Control Study

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

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World Journal of Gastroenterology
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World J Gastroenterol 2017 June 14; 23(22): 3964-3977

DOI: 10.3748/wjg.v23.i22.3964

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Molecular mimicry in *Helicobacter pylori* infections

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Author contributions: Chmiela M designed and wrote the manuscript; Gonciarz W wrote some parts of the manuscript and designed the figure.

Supported by the National Science Center grants, No. UMO-2013/09/N/NZ6/00805 and No. UMO-2015/17/N/NZ6/03490.

Conflict-of-interest statement: No potential conflict of interest.

Manuscript source: Invited manuscript

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Received: January 18, 2017
Peer-review started: January 21, 2017
First decision: February 9, 2017
Revised: May 16, 2017
Accepted: June 1, 2017
Article in press: June 1, 2017
Published online: June 14, 2017

Abstract

Gram-negative bacteria *Helicobacter pylori* (*H. pylori*) colonize gastric mucosa in humans and increase the risk of serious diseases such as gastric and duodenal ulcers, stomach cancers and mucosa associated lymphoid tissue lymphoma. The role of *H. pylori* infection in the pathogenesis of several extragastric diseases has been suggested including immune thrombocytopenic purpura, iron deficiency anemia, vitamin D deficiency, cardiovascular diseases, diabetes mellitus and dermatological disorders. Also neurological diseases and even lung cancer have attracted researchers concern. The relation between *H. pylori* infection and a growth retardation in children has also been suggested. Many mechanisms of molecular mimicry between *H. pylori* and the host have been proposed as a pathogen strategy to manipulate the immune system of the host in order to remain unrecognized and avoid eradication. A lot of effort has been put into the demonstration of homologous sequences between *H. pylori* and host compounds. However, knowledge about how often autoantibodies or autoreactive T lymphocytes induced during *H. pylori* infections cause pathological disorders is insufficient. This review provides data on *H. pylori* antigenic mimicry and possible deleterious effects due to the induction of immune response to the components common to these bacteria and the host.

Key words: *Helicobacter pylori*; Molecular mimicry; Anti-self response; Extragastric effects

Core tip: Molecular mimicry between *Helicobacter pylori* (*H. pylori*) and the host structures has been suggested as an effective mechanism of antibody production, potentially autoreactive. The chronic character of *H. pylori* infections increases the risk of such production and initiation or maintenance of *H.*

pylori related pathological disorders triggered by the host effector immune mechanisms during infection. The panel of components common to *H. pylori* and the host is still increasing and thus the risk of autoimmune complications is an open problem.

Chmiela M, Gonciarz W. Molecular mimicry in *Helicobacter pylori* infections. *World J Gastroenterol* 2017; 23(22): 3964-3977 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i22/3964.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i22.3964

INTRODUCTION

H. pylori pathogenicity - brief summary

Helicobacter pylori (*H. pylori*) a Gram-negative pathogenic bacterium, which has been described by Warren and Marshall in 1983[1], colonizes the gastric epithelium of humans (on average, 50% of the human population) and induces an excessive inflammatory response with or without symptoms (20% of cases). *H. pylori* infections possibly lead to different disorders such as: gastric and duodenal ulcers and, chronic gastritis, and even malignant diseases, including: mucosa-associated lymphoid tissue (MALT) lymphoma and gastric cancer[2-6]. Polymorphisms of the host genes encoding interleukins (ILs), including IL-1β, tumor necrosis factor (TNF-α) and cyclooxygenase -2 (COX2) have been suggested to increase the risk of infection and its severe consequences[7]. *H. pylori* strains have different genes encoding virulence factors that are important for disease development[8-10], which are either secreted, membrane-associated or translocated into cytosol of the host cells *via* the IV type secretion system, where they can affect the host cell functions[4]. *H. pylori* strains produce different adhesins, such as blood group antigen - binding adhesin (BabA), sialylated blood group - related adhesin (SabA), adherence - associated lipoprotein (AlpA/B) and outer membrane inflammatory protein (OipA), which promote close contact between the bacteria and the gastric epithelium[8-10]. Soluble factors such as urease and vacuolating cytotoxin (VacA) alter gastric cell survival and intercellular adhesion[11-16].

H. pylori CagA (Cytotoxin - associated gene A) is a highly immunogenic protein, which can trigger inflammatory responses in host gastric tissues, and it may influence the cell morphology, polarity, and proliferation; CagA also modulates the activity of immune cells and increases the risk of severe consequences, such as gastric ulcer and cancer[17-25]. Due to bacterial cell lysis, CagA and other *H. pylori* virulence factors can also be delivered to the gastric mucosa in a soluble form and affect the host immune cells infiltrating this milieu[24-27]. Moreover, *H. pylori* continuously produces phospholipid vesicles, which can be distributed by the circulation and function as a secondary extragastric source of CagA and other virulence factors[28-34]. Mucosal recognition of CagA is associated with the stimulation of epithelial cells that produce elevated levels of various cytokines, including IL-1β, IL-6 and IL-8, which is followed by the enhanced infiltration of activated neutrophils and severe mucosal inflammation that increases the risk of gastric cancer[19,35-38].

In addition, flagellin and especially lipopolysaccharide (LPS) were investigated to address their role in *H. pylori* pathogenesis *via* activation of NF-κB and chemokine expression[39]. Previous studies showed that *H. pylori* LPS possesses immunomodulatory properties that diminish the effectiveness of the phagocytosis, cytotoxic activity and the expansion of NK cells and T lymphocytes[40-42].

The interactions of *H. pylori* with host cells result in adherence, induction of inflammatory responses through cytokine/chemokine release, apoptosis or proliferation, which finally result in persistent colonization, severe inflammation, and disruption of the epithelial barrier function[43,44].

This process can enable the translocation of *H. pylori* virulence factors and inflammatory mediators into the circulation and promote or intensify the development of systemic inflammatory response and the possible clinical effects of *H. pylori* infections outside the stomach[45,46].

The role of *H. pylori* in some hematologic conditions has been considered, such as immune thrombocytopenic purpura (ITP), iron deficiency anemia (IDA), and vitamin B12 deficiency. The possible role of *H. pylori* infection in other hematologic diseases, such as non-Hodgkin lymphomas of the stomach, monoclonal gammopathy of undetermined significance, megaloblastic anemia and myelodysplastic syndromes, has been suggested[47]. The elevated risk of childhood leukemia and hemorrhage in patients with coagulation disorders due to *H. pylori* infection has also been considered. The effects of *H. pylori* on other disorders, such as cardiovascular diseases, diabetes mellitus, dermatological disorders, neurological disorders and even lung cancer, have also attracted attention of researchers[48-53]. Data obtained from these studies showed that the immune response induced by *H. pylori* may influence the clinical outcome of these disorders. Many seroepidemiological studies have shown that patients with coronary heart disease (CHD) produce anti-*H. pylori* antibodies[54-57]. A strong immune response triggered by *H. pylori* CagA - positive strains has been suggested to influence the development of atherosclerosis[58]. Many previous studies have stated that chronic infection with *H. pylori* has a significant influence on the immune system. Therefore, the possible mechanisms of *H. pylori* infections in the pathogenesis of the majority of extragastric diseases include chronic local or systemic inflammation and the

initiation of autoimmune responses[59].

CONCEPT OF TRIGGERING AUTOIMMUNE DISORDERS DUE TO MOLECULAR MIMICRY BETWEEN INFECTIOUS AGENTS AND HOST COMPONENTS

Molecular mimicry is a common strategy used by infectious agents to adapt to the host organism and avoid its immune response mechanisms. Molecular mimicry is defined as an antigenic and functional similarity between the second-row microbial structures and host molecules that leads to the production of auto-reactive antibodies, which may contribute to the development of autoimmune disorders. Similarities within and between linear amino acid sequences and spatial structures have been identifiedd[60-62].

Streptococcus pyogenes is one of the most intensely studied bacterial pathogens, that can trigger autoimmune diseases in genetically susceptible individuals. *S. pyogenes* is involved in the development of rheumatic fever and glomerulonephritis due to the induction of antibodies recognizing bacterial M protein and N-acetyl-β-D-glucosamine (GLcNAc) as well as human heart myosin[62,63]. Moreover, infections with Gram-negative bacteria, such as *Klebsiella pneumoniae* and *Campylobacter jejuni*, also stimulate the production of crossreactive antibodies that recognize the human leukocyte antigen (HLA)-B27 or gangliosides[62,64]. Additionally, certain viruses, such as the Epstein-Barr virus and the hepatitis B virus, share similar sequences with proteins in the central nervous system[65,66]. Molecular mimicry combined with the ability of T cells to evade the mechanisms of tolerance has been suggested as a potential mechanism implicated in the pathogenesis of various autoimmune diseases, including multiple sclerosis, diabetes mellitus and spondyloarthropaties[60,66-68].

MOLECULAR MIMICRY BETWEEN *H. PYLORI* AND HOST CELL COMPONENTS

The mechanisms by which *H. pylori* infections lead to various gastric and potentially extragastric disorders are still poorly understood. One concept indicates the role of autoimmune processes. Chronic exposure to *H. pylori* compounds may initiate autoimmune gastritis due to molecular mimicry between *H. pylori* structures and the host tissue. The hypothesis of the induction by *H. pylori* anti-self reactions was proposed after antibodies with reactivity to the gastric antral mucosa were detected in the sera of infected patients[69-71]. Many mechanisms underlying the molecular mimicry between *H. pylori* and the host have been proposed and many efforts have been made to identify homologous sequences between *H. pylori* and host polypeptides, including the P-type adenosine triphosphate (ATP)-ases CopA and CopP that are involved in heavy metal iron transport, 686-bp amino acid ATPase, VacA, and urease beta chain *vs* gastric H+K+-ATPase[72-75], heat shock protein (Hsp) A *vs* GroEs, HspB *vs* 60-kDa host Hsp[76], and hemagglutinin/protease (hap) *vs* carbonic anhydrase[77]. However, whether and how often the autoantibodies induced in response to *H. pylori* infection are involved in various post-infectious pathologies due to the pathogen - induced autoreactive T lymphocytes or antibodies is unclear. The examples of potential autoantigenic host targets for anti-*H. pylori* antibodies are listed in Figure 1.

H+/K+-adenosine triphosphatase as an autoantigen in autoimmune gastritis

Autoimmune gastritis/pernicious anemia is characterized by two phenomena: atrophy in the corpus and fundus of the stomach and autoantibody production against parietal cells (PC) and their secretory component called an intrinsic factor (IF)[78-80]. Anti-PC antibodies, which target H+/K+ ATPase, a gastric proton pump, have been detected in 60%-85% of patients with autoimmune gastritis, whereas antibodies to IF have been detected in 30%-50% of patients with autoimmune gastritis[81-83]. Chronic autoaggression to H+/K+ ATPase may diminish gastric acid secretion, and cause hypergastrinemia and anemia due to iron deficiency[84,85]. Pernicious anemia is also characterized by a vitamin B12 deficiency. Patients suffering from autoimmune gastritis are predisposed to gastric tumors and adenocarcinomas[86]. In patients with type 1 diabetes or autoimmune thyroid disease, the prevalence of autoimmune gastritis is approximately three-fold higher than that of the general population, in which such autoimmune disorder has the frequency of 2%[87]. CD4+ T lymphocytes, which recognize parietal cell H+/K+ ATPase, have been shown to be involved in the development of autoimmune gastritis. H+/K+ ATPase is released from parietal cells during normal cell turnover and is selectively captured and then processed by antigen - presenting cells[88,89]. Another possibility is that *H. pylori* infection may initiate the development of autoimmune gastritis and pernicious anemia through the activation of T lymphocytes that are autoreactive to H+/K+ ATPase due to the antigenic mimicry between gastric H+/K+ ATPase and *H. pylori* at the T cell level[90]. Antibodies to gastric H+/K+ ATPase and their secretory forms are produced by B lymphocytes in cooperation with CD4+ antigen-specific T lymphocytes[91,92]. The deleterious effects of autoantibodies can be a consequence of T cell perforin-dependent cytotoxicity and apoptosis initiated by interaction between the Fas receptor (Fas) an Fas ligand[71]. The role of chronic *H. pylori* infections in the development of atrophic gastritis has

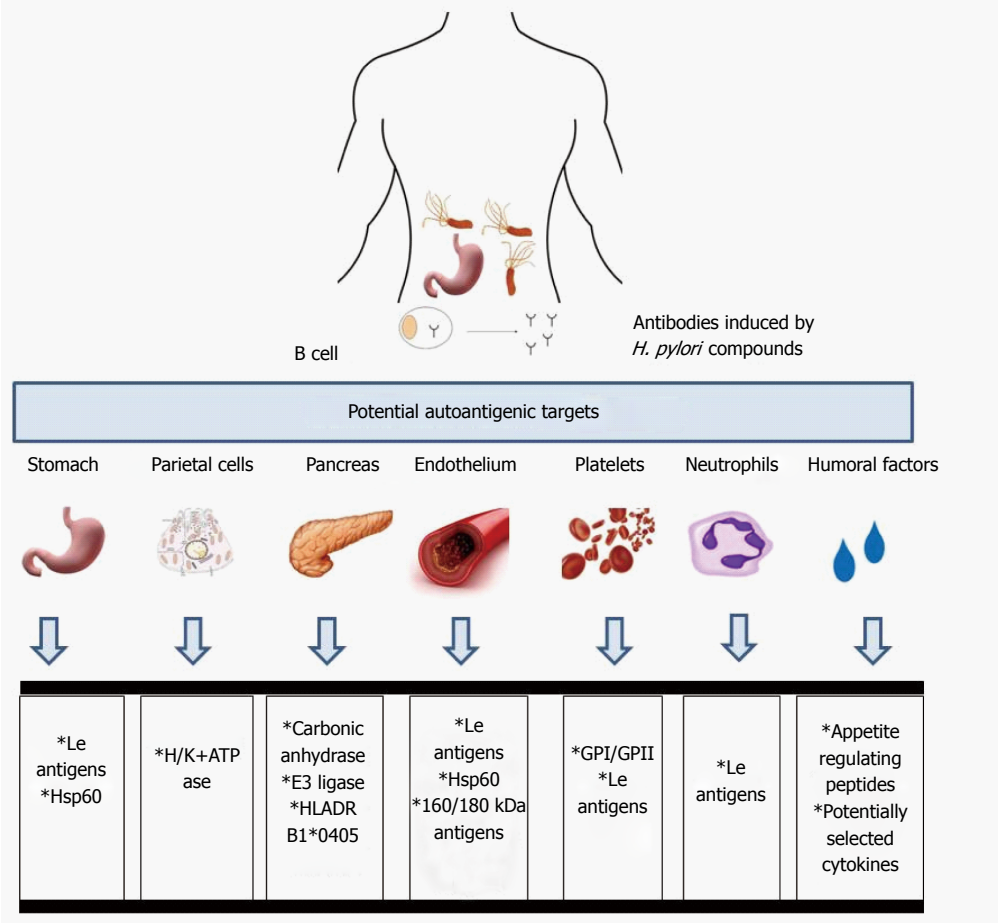

Figure 1 Hypothesis of autoimmune disorders due to molecular mimicry between *Helicobacter pylori* and the host components. Chronic exposure of the host immune system to *Helicobacter pylori* (*H. pylori*) components that have homologous sequences with the host cellular or soluble compounds may initiate the production of autoantibodies. However, how often the autoantibodies arising during *H. pylori* infection are involved in various post-infectious pathologies should be elucidated. The graph shows the examples of host targets for the antibodies induced by *H. pylori* components. GP: Glycoproteins; Hsp: Heat shock protein; H+/K+ ATPase: H+/K+-adenosine triphosphatase; HLA: Human leukocyte antigens; CCRL1: CC chemokine receptor-like 1; Le: Lewis antigens.

been suggested on the basis of the positive correlation between gastric autoantibodies and antibodies specific to *H. pylori* antigens in the majority of patients with pernicious anemia[69,75,93-95]. However, this association has not been confirmed in other studies[96,97].

Anti-Lewis antibodies induced by H. pylori lipopolysaccharide determinants

The presence of antibodies that react with the gastric mucosa in patients infected with *H. pylori* suggested that the autoantibodies induced by this pathogen may play an important role in the *H. pylori* - associated inflammatory response and cause deleterious gastric effects[75,94,98,99]. These antibodies could be stimulated by various Lewis (Le) antigens (Le^x, Le^y and $Le^{x/y}$) that are present in the LPS structure of many *H. pylori* isolates[99,100], and on human cells including polymorphonuclear leucocytes, gastric epithelial cells and endothelial cells. The LPS O-specific chain of the *H. pylori* reference strain NCTC (National Collection of Type Cultures) 11637 was found to possess determinants similar to the human Le^x blood group antigens**,** whereas LPS of the *H. pylori* MO19 strain contains determinants similar to human Le^y[101-103]. Other blood group antigens, including H type 1, Le^a, Le^b, nonfucosylated polylactosoamine (i-antigen), sialyl Le^x, and blood group A but not H type 2 have been detected in various *H. pylori* isolates. Additionally, strains bearing two or three blood group antigens in their LPS have been described[103-106]. The *H. pylori* LPS phase variation, which is defined as the random reversible change in phenotype in a range of blood group determinants, has been described for both reference and clinical strains[107,108]. During *H. pylori* infection different environmental and host factors including - gastric juice acidity may promote the selection of bacteria with the best phenotype in terms of virulence[109,110]. In a rhesus monkey model of *H. pylori* infection, the host Le^y phenotype of the gastric mucosa was shown to select the Le^y - positive phenotype of *H. pylori*, and the Le^x host gastric phenotype was shown to select the Le^x - positive bacteria[109]. Phase variations from Le^x to i-Ag and back to Le^x, from Le^x to Le^x plus Le^y, and from Le^x to Le^y and forming Le^a have been described[104,111-113]. The molecular mechanism of *H. pylori* LPS phase variation

depends on mutations in the genes encoding α3-fucosylotransferases, the activity of these proteins and their preference for carbohydrate residues that determine antigenic specificity[82,108,114-117].

Experiments performed with the use of anti-Le monoclonal antibodies induced by immunization of mice with *H. pylori* showed that these antibodies reacted with both murine and human gastric mucosa, foveolar and glandular epithelial cells and parietal cell canaliculi. The anti-Le^x monoclonal antibodies provoked by *H. pylori* were shown to react with polymorphonuclear leukocytes, gastric mucin and H+/K+ ATPase, which all express Le antigens[118]. However, it is unclear how anti-Le antibodies influence *H. pylori* adhesion and colonization of gastric mucosa in light of the results showing that the attachment of *H. pylori* to the human gastric epithelium is mediated by blood group antigens, including Le^b, Le^x and sialylated-Le^x[8,119-121]. One possible mechanism underlying this effect is the diversification of *H. pylori* in the human host through lipopolysaccharide phase variation due to the heterologous expression of the alpha 1,3-fucosyltransferase gene[107,117]. The role of anti-$Le^{x/y}$ antibodies in the pathogenesis of *H. pylori* - driven deleterious effects is controversial. It has been hypothesized that anti-Le antibodies initiated by *H. pylori*, if bound to the gastric epithelium, can cause complement - dependent cell lysis promoting an excessive inflammatory response[99]. In early studies, these antibodies were not detected at all or only found in a low number of serum samples from individuals infected with a *H. pylori*. Other studies, including our previous work, have revealed that humans may produce anti-Le^x antibodies, particularly those of the IgM class, in the absence of *H. pylori* infection or in the context of *H. pylori* - independent dyspepsia[118,122]. This finding indicates that anti-Le antibodies may be natural antibodies associated with the physiological autoimmunity required for the elimination of self-antigens. However, the incidence of this antibody production increases with age and, can be associated with the history of infections during the life of an individual[123]. The occurrence of anti-Le^x antibodies in the sera of subjects not infected *H. pylori* could be induced by other microorganisms, such as streptococci, *Eikenella corrodens* or *Acinetobacter actinomycetemcomitans* bearing Le^x determinants[124]. However, the possibility that *H. pylori* locally induces anti-$Le^{x/y}$ antibodies, which bind directly to gastric mucosal epitopes, and are absent in the serum, cannot be excluded[88,99]. Interestingly, the frequency of anti-$Le^{x/y}$ antibodies in the sera of patients infected with *H. pylori* and exhibiting gastritis symptoms, as well as in the patients with confirmed ischemic heart disease and *H. pylori* co-infection, was correlated with the increased occurrence of soluble $Le^{x/y}$-anti-$Le^{x/y}$ IgG immune complexes[123-125]. It is possible that the deleterious effects of anti-Le antibodies depend on their ability to bind ligands and form rather small immune complexes, which may be deposited locally in both gastric and endothelial tissues where they can promote the inflammatory response. Perhaps the severity of anti-Le antibody production in *H. pylori* - infected individuals is associated with higher exposure to Le antigens due to inflammation, damage to the gastric epithelium and/or vascular endothelial cells, and the migration and activation of immune cells. Since the expression of $Le^{x/y}$ determinants in *H. pylori* is related to the *cagA* status[126], anti-Le antibodies may increase the inflammatory effects on the gastric mucosa in association with *H. pylori* virulence proteins, such as CagA, VacA and urease. However, Zheng *et al*[127] showed that peptic ulcer disease was not related to *cagA* status, *iceA* (induced by contact with the epithelium) or *vacA* genotypes, but there was an association with increased expression of a combination of Le antigens in *H. pylori*. This finding suggests that gastric disorders related to *H. pylori* infection depend on a specific type of host-pathogen interactions. The bacterial Le determinants may promote the adaptation of bacteria to the host gastric mucosa, which allow them to evade the host immune response and establish a chronic infection, and tissue destruction *via* the induction of anti-Le autoantibodies. The complex strategy of *H. pylori* for survival in the gastric mucosa of the host involves both structural modifications of lipid A in LPS to diminish its endotoxic properties and the expression and variation of Le determinants that mimick host components[125].

Link between H.pylori infection and ITP

In 1988 Gasbarrini *et al*[128], showed that eradication of *H. pylori* resulted in regression of ITP. There are several potential mechanisms that combain *H. pylori* infection with ITP. One is molecular mimicry between *H. pylori* CagA protein and platelet glycoproteins: GPI and GPII[129-131]. In ITP patients infected with CagA positive but not CagA negative *H. pylori* strains a higher number of B lymphocytes producing anti-CagA antibodies that crossreact with the platelet specific peptides have been detected, which was correlated with the elevated levels of such antibodies in the patients sera[129,131]. A complement dependent mechanism of platelet destruction has been suggested[132,133]. Also Lewis antigenic determinants deposited on the surface of platelets may be recognized in ITP patients by anti-Le antibodies. During *H. pylori* infection the production of anti-Le antibodies is enhanced in response to Le antigens present in *H. pylori* LPS[123,130]. The infection can promote platelet aggregation, and the enhancement of expression of phosphatidilserine and p-selectin that may be involved in ITP development[133]. The platelet aggregation is also due to binding the von Willebrand factor by *H. pylori*[134]. Another possibility is that anti-*H. pylori* antibodies that link the platelet GP I protein with

phagocyte FcRIIa receptors may increase the clearance of platelets during phagocytosis. Bacterial LPS if deposited on the surface of platelets may enhance the immune phagocytosis[135]. Th1 lymphocytes activated during infection by *H. pylori* antigens are important for the maintenance of ITP[133]. Concerning the host genetic factors the HLA-DQB1*03 haplotype has been proposed as useful marker for prediction of the platelet response in *H. pylori* infected patients[136].

H. pylotri - related autoimmune hypothesis of cardiovascular disorders

H. pylori infections, especially those with CagA - positive strains, have been suggested to be associated with atherosclerotic vascular disease[58,137]. Patients suffering from CHD were found to be chronically exposed to *H. pylori* at a higher frequency than non-CHD individuals, which was shown by the high frequency and elevated levels of specific anti-*H. pylori* IgG and IgA antibodies[54,138,139] and strong inflammatory response[140], upregulation of biochemical markers, coronary lumen reduction, and elevated levels of low density lipoprotein, C-reactive protein, homocysteine, fibrinogen, plasminogen and inflammatory cytokines and the higher incidence of diabetes in *H. pylori* - infected individuals than in uninfected individuals[141-146]. However, in several studies, no associations between *H. pylori* seropositivity, exposure to CagA and CHD incidence have been found[46,147]. In the search for links between *H. pylori* infection and CHD, it has been suggested that *H. pylori* - induced antibodies with cross-reacting potency towards the host endothelium may play a role in the development and maintenance of atherosclerotic lesions. Autoimmune responses have been shown to participate in the initiation and progression of atherosclerosis[148]. Franceschi *et al*[149], have investigated whether antibodies against CagA cross-reacted with antigens of normal and atherosclerotic arteries, which would provide a possible link to the disorders observed during atherosclerosis. In this study, anti-CagA antibodies interacted with different parts of smooth muscle cells and endothelial cells present in the thin layer sections of atherosclerotic vessels. The antibodies recognized two vascular antigens of 160 and 180 K, which were present in both normal and atherosclerotic artery lysates and a 130 K protein from *H. pylori* lysates[149].

All *H. pylori* isolates produce urease, which can hydrolyze the urea present in the human stomach[150,151]. *H. pylori* urease is composed of a 26.5 kDa UreA subunit (β chain) and a 61.7 UreB subunit (α chain), which are encoded by the *ureA* and *ureB* genes, respectively[152,153]. Although the UreA subunit is the major immunodominant protein the UreB subunit has a higher number of epitopes recognized by anti-urease antibodies[154,155]. The occurrence of anti-urease antibodies was correlated with age and the immunoglobulin class and was linked with the severity of *H. pylori* - related disease symptoms. Superficial gastritis was correlated with a higher production of anti-urease IgA, whereas athrophy of the gastric epithelium was associated with elevated levels of anti-urease IgG immunoglobulins[156]. Recently, a hypothesis linking atherosclerosis and *H. pylori* - induced anti-urease antibodies has been suggested[157]. In the study by Arabski *et al*[158], a significant correlation between the level of antibodies recognizing the 8-mer synthetic peptide corresponding to the UreB minimal flap epitope of *H. pylori* urease and atherosclerosis symptoms was found. This *H. pylori* urease region exhibited similarity to the human CCRL1 (CC chemokine receptor-like 1) protein, which is expressed in heart tissue. Antibodies to *H. pylori* urease initiated during infection might be autoreactive due to the binding of the IKEDV motif in the CCRL1 host receptor. This antigen-antibody interaction may potentially accelerate complement - dependent tissue destruction and the inflammatory response in patients with atherosclerosis lesions and *H. pylori* infections[157,158].

H. pylori synthesizes the two heat shock proteins: HspA (GroES chaperonin or Hsp 10 homologue) and HspB (GroEL chaperonin or Hsp60 homologue)[76,159,160]. Both antigens reportedly induce autoimmune responses[161,162]. The study by Matusiak *et al*[139], supports the idea that chronic exposure to *H. pylori* in patients with CHD may result in an increase in the level of serum lipopolysaccharide - binding protein (LBP) and the production of antibodies against *H. pylori* Hsp B, which crossreact with human Hsp60. Both LBP and anti-Hsp 60 antibodies may facilitate the inflammation in the vascular endothelium. The pathological role of LBP may depend on the phenotype of the vascular endothelium, which exhibits proinflammatory features such as increased expression of pathogen recognition receptors. The involvement of anti-Hsp60 Igs in CHD-related deleterious processes can be explained by the antigenic mimicry and complement - dependent cell damage, which are possibly induced by these antibodies, similarly to the anti-*H. pylori* urease antibodies. Because the expression levels of Hsp proteins, including Hsp60, increases as a result of the inflammatory process in atherosclerotic lesions, it can be assumed that these proteins may be a target for anti-Hsp antibodies initiated by an infectious agent[148]. In regard to HspA, the clinical outcomes of *H. pylori* infection have been shown to be unrelated to HspA antigenicity or amino acid sequence variation[160]. However, age-specific responses to HspA in *H. pylori*-positive subjects have been found[163].

H. pylori infection and autoimmune pancreatitis

The association between *H. pylori* infection and insulin resistance has been suggested[146]. Recently, a significant homology between the human carbonic anhydrase II segment 5-255 and the α-carbonic

anhydrase of *H. pylori* segment 23-239, has been found, with 27% identity and 41% similarity[77]. Anhydrase is a key enzyme for the survival and growth of *H. pylori* in the gastric mucosa. In humans carbonic anhydrase II coordinates the physiological function of the pancreas. Moreover, the homologous regions contain the binding motifs of the HLA DRB1*0405[77]. These observations support the idea that *H. pylori* infection can trigger autoimmune pancreatitis in genetically susceptible individuals. In 2009, Frulloni *et al*[164] showed that in almost all patients with autoimmune pancreatitis there are antibodies against *H. pylori* plasminogen-binding protein (PBP). This PBP protein shows homology with ubiquitin-protein ligase E3 component n-recognition 2, which is an enzyme highly expressed in the acinar cells of the pancreas. This could be another example of *H. pylori* and host molecular mimicry triggering autoimmune pancreatitis.

H. pylori - host antigenic mimicry and growth retardation in children

The relationship between *H. pylori* infections and growth retardation in children is poorly understood. Growth retardation may result from appetite disorders, abnormal metabolism and iron deficiency[165]. Infection with *H. pylori* causes gastrointestinal bleeding, abnormal absorption of iron due to the impaired gastric acid and insulin secretion, and vitamin C uptake. The mechanism driving anemia in children infected with *H. pylori* may be antigenic mimicry. *H. pylori* has an iron-binding protein similar to ferritin, which prevents iron excess. The infection also causes an increase in the concentration of iron-binding lactoferrin in the stomach epithelium[165]. Recent studies indicate the role of the immune system in controlling behaviors related to food intake by producing autoantibodies against peptides and neuropeptides regulating appetite, which may result in a reduction in height and weight[166].

The gastrointestinal microflora, including *H. pylori* may be a source of antigens, which are similar to appetite - regulating peptides. Thus, the bacterial antigens are potentially able to stimulate the immune system of the gastrointestinal tract to produce autoantibodies that are cross-reactive with many of the appetite -regulating peptides and that modify the actions of these peptides. In the sera of pediatric patients with short stature the autoantibodies against 14 key hormones and peptides regulating appetite such as leptin, ghrelin, orexin, and alpha-melanocyte-stimulating hormone (α-MSH), have been detected[166]. These antibodies are also present in healthy subjects, which suggests physiological role for these antibodies in the regulation of hunger and satiety. A number of common sequences between these peptides and proteins of microorganisms have been identified, including antigenic similarity between leptin and the intestinal microflora proteins of *Lactococcus lactis*, *Escherichia coli*, *Lactobacillus bacteriophage* and representatives of *Candida* and *Aspergillus*. The sequence homology of α-MSH and the components of pathogenic *E. coli*, *H. pylori*, *Clostridium tetani*, and *Candida albicans* has also been demonstrated. Regulatory peptides are signaling molecules, and autoantibody blocking of their sequences may alter their biological activity. A recent study highlighted the impact of *H. pylori* on the secretion of ghrelin and leptin[167]. Patients infected with *H. pylori* have been shown to have a significantly lower level of leptin and ghrelin in the plasma. The ghrelin concentration was also lower in the mucous cells of the stomach. After eradication of the infection, the level of ghrelin rose again. However, other authors did not confirm this result[168]. In the studies carried out on a group of Polish children, it was shown that the levels of gastrin in the patients infected with *H. pylori* were significantly higher, whereas the levels of ghrelin and leptin were lower than those of the controls[169]. Growth failure in children due to anemia occurs more often in patients infected with *H. pylori cagA*+ than *cagA*- strains. It has been shown that platelet glycoprotein and the CagA protein are similar and that many patients infected with *H. pylori* with signs of thrombocytopenia have possess anti-platelet antibodies[165]. These results suggest a role for the CagA protein in the development of systemic pathological processes in children infected with *cagA*+ *H. pylori* strains. Further studies are needed to assess the prevalence and the levels of antibodies against the common sequences for CagA protein and peptides regulating appetite in children with short stature. These sequences have been identified by bioinformatic analysis of leptin, ghrelin, visfatin and resistin, which regulate appetite, energy homeostasis, and potentially the immune system[167,170-173]. The release of these proteins is often stimulated by inflammatory processes, growth and gonadal hormones. The results of experiments conducted with serum samples from children with idiopathic short stature and growth hormone deficiency showed that some of the children that were also infected with *H. pylori* and/or exposed to *C. albicans* have antibodies against ghrelin, leptin, orexin A and α-MSH, which may potentially disturb the physiological functions of these molecules[174,175]. This result is potentially due to molecular mimicry between antigens of these microbiota and the mentioned peptides. However, further studies are needed to elucidate this suggested relation.

Newly described gastric potentially autoantigenic proteins as possible targets for antibodies induced by *H. pylori*

Recently, amino acid identity between additional autoantigens derived from the gastric mucosa and gastric adenocarcinoma cells (AGS) and several *H. pylori* proteins has been identified. A proteomics

investigation of anti-gastric autoantibody profiles in the sera of 300 Korean adults infected with *H. pylori*, revealed nearly forty autoantigenic proteins, including nicotinamide adenine dinucleotide phosphate (NADP+) alcohol dehydrogenase, alpha enolase, gastrokine-1, gastric triacylglycerol lipase, Hsp70 kDa protein 1, and peroxiredoxin-2. These proteins were detected in the gastric mucosal tissue[59]. The programmed cell death 6 - interacting protein, serum albumin and T-complex protein 1 subunit gamma were identified in the AGS cells. Several proteins such as albumin, alpha-enolase, annexin A3, cytoplasmic actin 1, Hsp - like 71 kDa protein and leukocyte elastase inhibitor, were detected in AGS cells and gastric mucosal tissue. Furthermore, the alpha-enolase, glutathione S-transferase P, Hsp - like 71 kDa protein, Hsp70 kDa protein 1, mitochondrial Hsp60 kDa, peroxiredoxin-2, 78 kDa glucose-regulated protein precursor, tyrosine-protein phosphatase non-receptor type 11 and tryptophan-aspartic acid repeat-containing protein (WD), showed 60% or even higher amino acid positivity[59]. These newly described gastric proteins may have the ability to control and prevention gastroduodenal disorders linked to *H. pylori* infections, such as chronic gastritis, gastroduodenal ulcers, atrophic gastritis and gastric cancers. However, their role in the pathophysiology of these disorders needs to be examined.

Gastric tissue ulceration initiated by *H. pylori* is related to the elevated production of alarming molecules, including IL-33, which may function as a classic cytokine or transcription factor[176]. IL-33 is suspected to alert the immune system to restore epithelial cell homeostasis. However, IL-33 has also been suspected to play an emerging role in autoimmune diseases[177]. Bioinformatic analysis indicates homology between the amino acid sequences of *H. pylori* CagA and human Hsp60, as well as IL-33. Hypothetically, both host Hsp60 and IL-33 can be targeted by antibodies induced during *H. pylori cagA*+ infections, which may affect gastric inflammatory reactions.

Although the homologous sequences of *H. pylori* and several new host targets have been demonstrated by computer and proteomic analyses, more research is needed to demonstrate the role of these homologous sequences in development of pathological processes due to autoimmune responses initiated by *H. pylori* components.

DISCUSSION

In light of this review, we hypothesize that *H. pylori* possessing antigens that are similar in structure to human cells, tissues and some humoral compounds, which play an important structural and physiological role, through induction of humoral and possible cellular immune responses, may drive tissue destruction and the development a pathological inflammatory response. Chronic exposure of specific memory cells to these *H. pylori* compounds enables their sustained stimulation and transformation into effector lymphocytes, which may be involved in the autoimmune-mediated tissue destruction. Further studies and deeper analyses are necessary to demonstrate the autoimmune potential of specific *H. pylori* antigens.

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P- Reviewer: Balaban YH, Franceschi F, Vilaichone RK, Yamaoka Y, Youn HS **S- Editor**: Gong ZM **L- Editor**: A **E- Editor**: Wang CH

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ISSN 1007-9327