

Helicobacter Pylori Induced Gastric Inflammation, Ulcer, and Cancer: A Pathogenesis Perspective

Neelapu NRR*, Nammi D, Pasupuleti ACM and Surekha C

Department of Biochemistry and Bioinformatics, School of Life Sciences, GITAM Institute of Science, GITAM University, Rushikonda Campus, Visakhapatnam, Andhra Pradesh, India

*Corresponding author: Nageswara Rao Reddy Neelapu, Department of Biochemistry and Bioinformatics, School of Life Sciences, GITAM Institute of Science, GITAM University, Rushikonda Campus, Visakhapatnam, Andhra Pradesh, India, Phone: +91-891-2840464; Fax: +91-891-2790032; E-mail: nrneelapu@gmail.com; nrneelapu@gitam.edu

Rec date: September 15, 2014; Acc date: October 1, 2014; Pub date: October 8, 2014

Copyright: © 2014 Neelapu NRR, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Helicobacter pylori infection induces gastric inflammation, ulcer, and cancer. *H. pylori* infection is coordinated in a cascade manner that helps it to colonize in the host. Colonization of bacterium starts by adapting itself to the harsh acidic environment in the stomach. *H. pylori* has the necessary machinery to neutralise the pH of its surroundings. It also has the ability to sense the pH of its surroundings and move towards the less acidic region. *H. pylori*'s next hurdle is gastric mucosal barrier in the stomach and it has the capability to overcome this gastric mucosal barrier. Once the gastric mucosal barrier is weakened, pathogen uses different adhesion molecules to adhere to the epithelial lining of the stomach. Pathogen then establishes interaction with the host using several toxins that indirectly leads to development of inflammation or gastritis. Prolonged inflammation damages epithelial cells leading to ulcers in the stomach. Genetic changes in the host cell due to *H. pylori* infection leads to development of gastric cancer. The present paper reviews in detail *H. pylori* induced gastritis, gastric ulcers and gastric cancer.

Keywords: Cag PAI, Gastritis, Inflammation, Ulcers, Gastric cancer, Apoptosis cytokines, Chemokines, *Helicobacter pylori*

Introduction

Helicobacter pylori (previously known as *Campylobacter pylori*) is about 3 µm long and 0.5 µm in diameter, microaerophilic (requires oxygen), neutralophilic (adapting to highly acidic environment) helix-shaped (curved rod), gram negative bacteria colonizing upper gastrointestinal tract. Conservative thinking was that no bacterium can live in the human stomach as its pH is acidic in nature (~1). Research to identify spiral shaped bacteria in the lining of human stomach was initiated by a group of German scientists in 1875 [1]. Akin Bizzozero [2] detected similar bacteria in the stomach of dogs. Professor Walery Jaworski in 1899 investigated and proposed the possibility of being an organism involved in gastric diseases [3]. Several studies conducted over a period of time concluded that microbes or stress or spicy food are responsible for ulcers and gastric diseases. Warren and Marshall [4] identified, visualized, and cultured *H. pylori* in *in vitro* conditions and declared that stomach ulcers and gastritis are mostly due to *H. pylori*, and not due to stress and spicy food. Dr. Barry Marshall administered himself *H. pylori* culture through an oral route to demonstrate the connection between gastritis and *H. pylori*. After 10 days, Dr. Barry Marshall revealed the signs of gastritis by endoscopy suggesting that *H. pylori* is the causative agent of gastritis. Warren and Marshall [4] also suggested that antibiotics can be employed for effective treatment of gastritis, for which they were awarded Noble Prize in Medicine or Physiology in the year 2005. Blaser [1] hypothesized that colonization of *H. pylori* in stomach is beneficial though its connection with gastritis was well established [5]. Blaser [1] also proposed it to be 'a member of the normal flora of the stomach'. Colonization of *H. pylori* in stomach influences systemic immune responses and reduces acid reflux disease [1], asthma [6], dermatitis

[6], esophageal cancer [1,6,7], gastroesophageal reflux disease [1,7], inflammatory bowel disease [6], obesity [8,9], rhinitis [6] and type II diabetes [8,9]. Chen and Blaser [10] asserted Blaser's hypothesis that *H. pylori* is a member of the normal flora of the stomach' by demonstrating the association between *H. pylori* colonization and lower incidence of childhood asthma. Whatever may be the consequences of colonization of *H. pylori* in stomach a positive effect by reducing diseases or undesirable effect by causing gastritis; association between *H. pylori* and host is essential.

Association between *H. pylori* and its human host was estimated to be around 60,000 years ago [11]. Simulations based on the genetic diversity data established the fact that association between *H. pylori* and its human host was first established in the birth place of modern human in Africa. *H. pylori* then diverged along with modern human from the birth place.

S. No	Country	Rank	% of rate of incidence	Year	Reference
1	Republic of Korea	1	41.8	2012	[17]
2	Mongolia	2	32.5	2012	[17]
3	Japan	3	29.9	2012	[17]
4	Guatemala	4	23.7	2012	[17]
5	China	5	22.7	2012	[17]
6	Tajikistan	6	21.7	2012	[17]
7	Kazakhstan	7	21.6	2012	[17]
8	Kyrgyzstan	8	21.4	2012	[17]
9	Albania	9	20.1	2012	[17]

10	Belarus	10	18.8	2012	[17]
11	Turkmenistan	11	18.2	2012	[17]
12	Costa Rica	12	17.3	2012	[17]
13	Bhutan	13	17.2	2012	[17]
14	Honduras	14	17	2012	[17]
15	Ecuador	15	16.9	2012	[17]
16	FYR Macedonia	16	16.5	2012	[17]
17	El Salvador	17	16.4	2012	[17]
18	Viet Nam	18	16.3	2012	[17]
19	Russian Federation	19	16	2012	[17]
20	Peru	20	15.8	2012	[17]

Table 1: International statistics on gastric cancer

Phylogenetic analysis established the following lineages of *H. pylori* that diverged during the course of evolution—Africa 1 (includes isolates from West and South Africa), Africa 2 (includes isolates from South Africa), NE Africa (includes isolates from North East Africa),

Amerind (includes isolates from Native Americans), Asia 2 (includes isolates from Bangladesh, Malaysia, North India and Thailand), East Asia (includes isolates from East Asians), Europe (includes isolates from Europe, Middle East, India), Maori (includes isolates from Taiwanese Aborigines, Melanesians and Polynesians), and Sahul (includes isolates from Australian Aborigines, and Papua New Guineans). Ancestors for the above lineages are ancestral East Asia, ancestral Africa 1, ancestral Africa 2, ancestral Europe 1, ancestral Europe 2 and ancestral Sahul [12].

Diversity among the *H. pylori* isolates established the fact that world's human population is infected with *H. pylori* and is the most widespread infection in the world. Living standards of the country, age of the host infected with *H. pylori* can be the factors that influence the possible outcome of the infection. Infection rate is high in underdeveloped countries followed by developing countries and developed countries [13]. Socioeconomic factors, hygiene standards, and wide spread of antibiotics can be attributed to the differences in the infection rates in different countries [14,15]. Age at which host is infected with the bacterium also influences outcome of the infection. High risk of gastric ulcer and cancer was observed in individuals who were infected at an early age than individuals who were infected at a later age [16-18]. The age standardised rate of gastric cancers in all the countries (Tables 1 and 2) explains the above trends on age. Statistics revealed that gastric cancer is the second most common cancer worldwide.

S. No	Name of the place	Rank in Male	AAR in Male	Rank Female	AAR in Female	Year	Reference
1	Chennai	1	13.6	3	6.5	1990-96	[18]
2	Bangalore	1	9.5	6	5.1	1990-96	[18]
3	Mumbai	5	6.4	7	3.2	1990-96	[18]
4	Bhopal	9	3.9	9	2.5	1990-96	[18]
5	Delhi	10	3.4	12	1.8	1990-96	[18]
6	Barshi	15	1.2	6	0.8	1990-96	[18]

Table 2: Gastric cancer statistics in India

H. pylori is tested if peptic ulcers disease, MALT lymphoma, dyspepsia were reported [19]. Several methods that are in use to test the existence or association of *H. pylori* with gastrointestinal disorders are endoscopy, biopsy, histological examination and microbial culturing [19]. If, *H. pylori* is cultured, they can be visualized by Gram stain, acridine-orange stain, Giemsa stain, haematoxylin-eosin stain, and Warthin-Starry silver stain. *H. pylori* can also be visualized using phase-contrast microscope. The other tests that are used are rapid urease, ELISA, blood antibody, and stool antigen tests [20]. Proton pumps, H2 antagonists, and antacids were initially used in treatment against *H. pylori* [21,22]. Standard first line therapy to treat *H. pylori* consists of triple therapy proton pump inhibitor omeprazole, antibiotic clarithromycin and amoxicillin. Alternative proton pump inhibitors are pantoprazole and rabeprazole; and alternate antibiotic for clarithromycin is levofloxacin and for antibiotic amoxicillin is metronidazole [23-25]. When initial therapy failed due to antibiotic resistance, alternative strategy such as quadruple therapy is implemented in the form bismuth colloid which includes bismuth subsalicylate [26,27]. Rising antibiotic resistance has driven the

research to identify new drug targets [28,29] and drugs [29]. Alternative therapeutic strategy such as 'routes of immunization' to provide immune protection in the form of vaccination to control *H. pylori* is also in trial [30]. New vaccines or drugs can be developed if we can better understand the pathogenesis of *H. pylori* at different stages such as adaptation of *H. pylori* to the acidic environment in the stomach, protection from oxidative stress induced by host, adhesion of the pathogen to the stomach, gastritis, ulcer, and gastric cancer.

Pathogenesis of the *Helicobacter pylori*

H. pylori is linked gastric carcinoma, gastric adenocarcinoma, gastric ulcer, gastritis and MALT lymphoma. *H. pylori* is contagious, where the person-to-person transmission is either by the fecal-oral or oral-oral route. *H. pylori* infection and pathogenicity is well connected and coordinated by different mechanisms to adapt to the acidic environment in the stomach; to attack the stomach wall by weakening the gastric mucosal barrier; using different molecules to adhere the host stomach lining; protecting itself from oxidative stress; inducing

gastritis or inflammation, formation of ulcers, and inducing gastric cancer.

Mechanisms of adaptation to the acidic environment in the stomach

The neutralophilic motile bacterium *H. pylori* has developed several strategies to minimize its exposure to low pH so that it can flourish well in the gastric environment of the host. *H. pylori* migrates from antrum to fundus to colonize in the host. The pH in the stomach varies widely, in the absence of food (pH is ~1.0) and in the presence of food (pH is ~5.0).

H. pylori has the adeptness to sense chemicals in the surrounding environment, and pH is an important cue (Figure 1). Bacteria recognize and act in response to these chemical signals using chemoreceptors. Four chemoreceptors TlpA, TlpB, TlpC, and TlpD and several polar flagella are reported in *H. pylori*. Chemoreceptors allow the bacteria to swim in case of attractant and stop in case of repellent [31,32]. Sweeney et al., [33] established the structure of chemoreceptor TlpB's and proposed the mechanism by which *H. pylori* sense pH. TlpB is a member of MCP superfamily of transmembrane receptors, containing two transmembrane helices with an extracellular sensing Per-ARNT-Sim (PAS) domain popularly known as universal signalling fold. Active site of this domain contains a molecule of urea. This domain along with urea is responsible for detecting ligands directly or indirectly via interactions with periplasmic proteins. Transmembrane helices on the cytoplasmic side are helical with a histidine kinase adenyl cyclase, methyl binding protein, phosphatase (HAMP) domain. Followed by a helical domain, that binds to the segment CheA/CheW histidine autokinase complex. At neutral pH, Asp114 in the active site is negatively charged and accepts two hydrogen bonds from the amide nitrogen atoms of cofactor urea, thereby binding and stabilising the fold of PAS domain. The state of the periplasmic domain is relayed through the transmembrane region affecting the phosphorylation of CheA, in turn controlling the downstream components of flagellar motor and its activity to guide stopping behaviour. Whereas, in the case of high pH Asp114 in the active site is highly protonated by weakening or disrupting binding of cofactor urea. Signal is relayed and guides flagellar motor to moving behaviour.

Once the pH is sensed by the chemoreceptors, *H. pylori* has two mechanisms to adapt to the acidic environment. The first mechanism of *H. pylori* is to change the pH of its surroundings and the second mechanism is to move towards the less acidic region. The pH of its surrounding environment is changed by urease and is coded by urease gene cluster ure A, B, I, E, F, G, and H [34]. Urease structural subunits are coded by ure A and B; followed by assemble of inactive urease structural subunits into active urease by incorporating nickel using ure E, F, G, and H [35]. Whereas, ure I encodes a pH gated urea channel to increase the access of urea to intrabacterial urease in low pH conditions [36]. Intrabacterial urease activity generates carbon dioxide and ammonia buffering the cytoplasm and periplasm of the organism [37]. Urease deletion mutants were not able to colonize the stomach and failed to survive in the acidic environment [38]. Followed by activation of mechanisms to sense and change the pH of its surroundings, *H. pylori* tends to move towards the less acidic region.

Stomach lining composes of mucous layer, followed by epithelial cells and connective tissue respectively. Mucous layer is towards the lumen interface and epithelial cells and connective tissue are underneath the mucous layer. pH at the mucous lumen interface and

at the mucous epithelial cells is ~2 and ~5 to 6 respectively. So, *H. pylori* uses its flagella to tunnel into the mucous and move towards the less acidic region. Thus, bacterium is able to move from the acidic pH at mucous lumen interface to the neutral pH at the mucous epithelial cells interface. It can be concluded that *H. pylori* is migrating from the stomach lumen via mucous layer to the epithelial cells to colonize as the pH of the epithelial cells is neutral.

Attacking the stomach wall—gastric mucosal barrier

Colonization of *H. pylori* is different in different individuals. Based on the acidity of the stomach bacterium can colonize mucous, or epithelium inner surface, or inside the epithelial cells or at pyloric antrum or at fundus or whole lining of the stomach or rest of the stomach. Colonization along the whole lining of the stomach, or at pyloric antrum, or at fundus can be due to normal or reduced amounts of acid secretion; large amounts of acid secretion; and to avoid acid secreting parietal acids respectively. Colonization of *H. pylori* along the lining of stomach or in the mucous or epithelial cells is possible only when gastric mucosal barrier is weakened. Gastric mucosal barrier protects gastric mucosa from a variety of damaging agent's such as gastric acid, pepsin, refluxed bile and pancreatic juice, certain foods, range of temperatures, hyperosmolar and abrasive substances, bacterial toxins and damaging drugs. Gastric mucosal barrier is collection of anatomical, physical and chemical processes that protect the gastric mucosa. The eight components of the gastric mucosal barrier are (1) tight junctions of the epithelial cells (2) restitution a process which gastric epithelial cells change shape (3) secretion of mucosal bicarbonate (HCO₃⁻) (4) hydrophobic nature of the apical membrane of the gastric epithelial cells (5) balance of local acid-base and gastric mucous blood flow (6) production and secretion of gastric mucosa (7) regulation and protective effect of mucosal prostaglandins and (8) basal lam. Though the role of *H. pylori* in damaging gastric mucosal barrier is not yet known, there might be some unknown mechanism contributing to weakening of gastric mucosal barrier that helps in colonizing bacterium in the mucous [39]. *H. pylori* may mediate the weakening of gastric mucosal barrier via toxin VacA, cytokines, gastrin release probably by loosening the protective mucous layer, disruption of mucous layer, and alterations in mucous glycoproteins respectively.

Adhesion of the pathogen to the stomach

H. pylori adheres to the epithelial cells with the help of adhesins such as BabA and SabA. Adhesins bind to carbohydrates and lipids of epithelial cell membrane [40]. BabA and SabA binds to Lewis b antigen and sialyl-Lewis X antigen expressed on epithelial cells and gastric mucosa respectively [41,42]. In addition to these proteins adherence is assisted by a group of proteins such as AlpA, AlpB, HopZ, and OipA [43]. Gastritis, ulcer formation and gastric cancer are three events which run parallel (Figure 1).

Inflammation or gastritis induced by *H. pylori*

Several mechanisms are proposed to describe the pathogenicity of *H. pylori*: change in expression of host genes, infection-induced cell proliferation, loss of polarity and elongation of cell, cell-cell junctions degradation, decrease in acid secretion [44] and inflammation. Cytotoxin associated gene pathogenicity island (cag PAI) with a size of 40 Kbp contains 27 genes encoding for T4SS pilus which is responsible for pathogenicity and inflammation. Cag PAI encodes for genes CagA, VacA, 11 VirB proteins (VirB1- VirB11) and coupling protein (VirD4). Core components or putative channel is formed by Vir B6-B10; pilus associated components is formed by VirB2, VirB3, and VirB5; VirB4

and VirB11 are the energetic components; VirB1 is a muraminidase enzyme which lyse murien at a particular location to establish T4SS pilus assembly. CagY (VirB5 orthologue), Cag I, L, Y, and VirB proteins form the appendage of pilus to secrete CagA, VacA and peptidoglycan into the host [45].

CagA when injected into the host epithelial cells, it is phosphorylated and activated by src kinase and host proteins to modify cellular responses [46]. Cell focal adhesions are disrupted by CagA by binding and activating SHP2 phosphates [46]. Normal epithelial architecture is disrupted when polarity regulator PAR1b/MARK2 kinase is inhibited by CagA leading to loss of polarity in epithelial cells [46]. Another surface receptor protein in *H. pylori* Toll like receptor (TLR)-2 disrupts adherin junctions within gastric epithelial cells. TLR-2 activates protease calpain cleaving E-cadherin and allows increased β -catenin signalling to disrupt adherin junctions [47].

H. pylori infection leads to inflammation at the site of infection by inducing proinflammatory cytokines. Peptidoglycan of pathogen enters the host cell and stimulates intracellular pathogen receptor Nod1, to signal and activate NF- κ B and AP-1 to induce cytokines such as interleukins. Interleukins (IL)-1, IL-6, IL-8, TNF- α , and RANTES are the inflammatory molecules upregulated in the host stomach. Apart from cytokines, chemokines like granulocyte-macrophage colony stimulating factor (GM-CSF), cyclooxygenases (COX-2), Reactive Oxygen/Nitrogen Species (RONS), *H. pylori* neutrophil activating protein (HP-NAP) are stimulated and activated during inflammation. Beales and Calam [48] found that infection of *H. pylori* stimulates GM-CSF when tested on human gastric epithelial cell lines. *H. pylori* infection also leads to activation of AP-1 to induce COX-2 and nitric acid synthase [49]. COX-2 induces prostaglandin synthesis (PGE)-2 [49]. *H. pylori* nitric acid synthase [49], LPS [50], arginases and host arginase II [51] produce, upregulate, and modulate nitric oxide species respectively. Vacuolating cytotoxin (Vac) A [52] and HP-NAP [53] induce ROS production at the site of infection. Huang et al., [52] demonstrated that Vac A induces ROS damage in mitochondrial DNA of gastric epithelial cells. Vac A interact with a number of host surface receptors to trigger responses such as pore formation, cell vacuolation, endolysosomal functions modification, immune inhibition and apoptosis [54-56]. HP-NAP is secreted and passes through the epithelial cell to reach lamina propria to induce ROS from neutrophils and monocytes and also to stimulate production of other chemokines such as CXCL8, CCL3, and CCL4 to attract or recruit other leucocytes [52,57,58]. Virulence factors such as γ -glutamyl transpeptidase, VacA and cholesterol α -glucosides modulated responses of T cells.

Protection from oxidative stress

Pathogenesis of *H. pylori* is dependent on its ability to survive in the vulnerable oxidative stress environment apart from other factors such as acidity, peristalsis and phagocytosis [59]. Oxidative stress induced by *H. pylori* when it colonizes host is lethal leading to DNA damage in the genome of *H. pylori* [60]. Many pathogens including *H. pylori* have acquired the ability to survive DNA damage induced by oxidative stress by transformation mediated recombination DNA repair for successful infection of the pathogen [61]. While many pathogens are competent for transformation only in certain environmental conditions such as starvation, *H. pylori* is competent throughout the growth [62]. *H. pylori* is exposed to double stranded DNA damage and natural transformation has increased with DNA damage [62]. Mutants of RecA, Rec N, RuvC, and AddAB were unable to colonize the human

host with increased sensitivity to DNA damaging agents and oxidative stress [62-64].

Formation of ulcers

When bacteria colonize the stomach, inflammation induces G cells of the antrum. G cells secrete hormone gastrin, which travels to parietal cells of the fundus via blood stream [5]. Gastrin stimulates secretion of the acid from the parietal cells and also increases the number of parietal cells. Increased load of acid damages epithelial cells of the duodenum resulting in ulcers [65].

Gastric cancer

Inflammatory cells produce cytokines such as metalloproteinases (MMPs), prostaglandin E2 (PGE2) and RONS, which in turn augment and prolong the inflammatory cascade (cytokines induce PGE2 and MMPs induce RONS). These inflammatory mediators disregulate DNA repair enzymes thereby leading to microsatellite instability (MSI). Inflammatory mediators also lead to defective mitotic checkpoints, induce directly or indirectly double stranded breaks (DSB) and deregulate HR pathway of DSB repair leading to chromosomal instability (CI). MSI and CI induce genetic diversification randomly leading to activation of oncogenes and inactivating tumor suppressor genes [66] (Figure 1).

LPS, peptidoglycan, and CagA of *H. pylori* activate transcription factor NF- κ B which is essential to activate innate and adaptive immune responses against pathogens. Sustained and constitutive expression of NF- κ B results in chronic inflammation and cancer [67]. NF- κ B signalling needs to be turned off properly to avoid prolonged and detrimental inflammatory responses. Cell utilizes many mechanisms at multiple levels for termination of NF- κ B signalling. I κ B α synthesis and cylandromatosis (CYLD) expression mechanisms are lost or overpowered in cancer by downregulation of NF- κ B signalling. Other mechanism by which NF- κ B is turned off is by direct ubiquitination and degradation of NF- κ B [68]. CagA and COX-2 were known for cell proliferation, prostaglandin biosynthesis and angiogenesis. Cag A binds to E-cadherin interfering β -catenin regulation, transdifferentiation of numerous cell lineages and increased cell proliferation [69]. Mitogen inducible cyclogenases-2 (COX-2) was reported to induce prostaglandin biosynthesis and angiogenesis in human gastric cancer tissues. COX-2 overexpression also correlated with metastatic involvement of the lymph nodes [70]. COX-2 expression correlated with microvessel density. VacA induced Reactive Oxygen Species (ROS) damage in mitochondrial DNA of gastric epithelial cells is studied by Huang et al., [53].

Though the information on activation of oncogenes is not well studied, several papers reported on inactivation of tumor suppressor genes after the *H. pylori* infection. Inactivation of the tumor suppressor genes-RUNX3, p53, ASPP2, TFF1, TFF2, TFF3, GKN1 and GKN2 promoted gastric carcinogenesis. Cag A induces proteasome-mediated degradation that inactivates gastric tumor suppressor gene RUNX3 [71,72]. Hypermethylation of promoter of RUNX3 also leads to gene silencing [71,73]. Cag A also induces proteasome-mediated degradation of p53 to modulate and ASPP2 tumor suppressor genes [74].

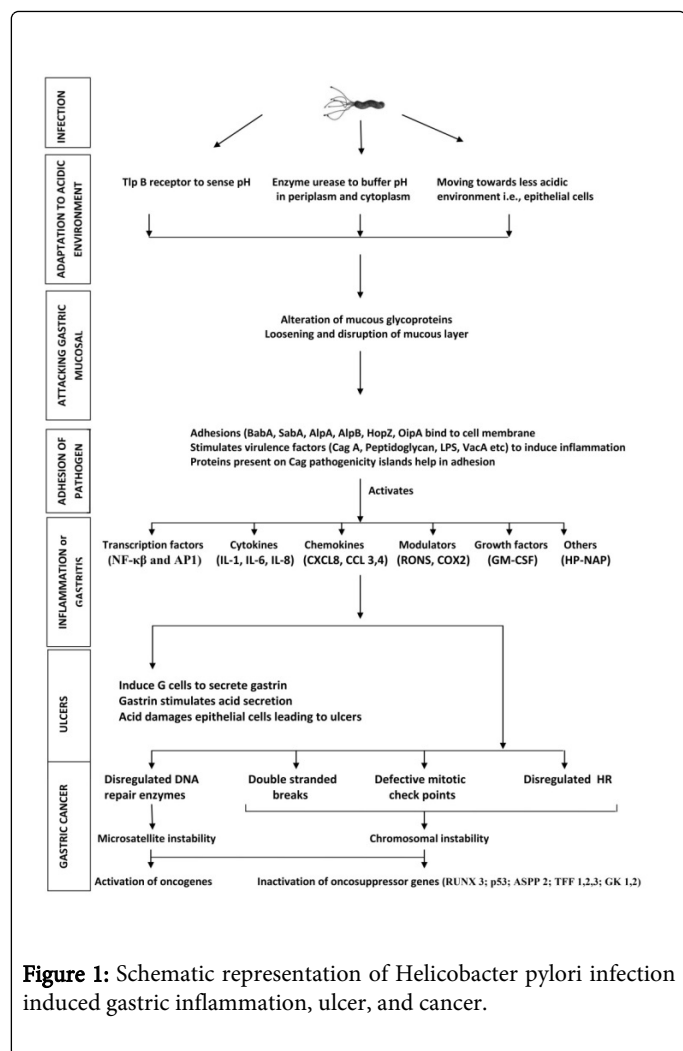


Figure 1: Schematic representation of *Helicobacter pylori* infection induced gastric inflammation, ulcer, and cancer.

Trefoil factor family proteins (TFF1,2,3) regulate mucosal repair and suppresses tumor formation in stomach. Deficiency of tumor suppressor genes TFF1 and genetic ablation of gene TFF2 revealed the protective role of TFF proteins and their reduction in promoting gastric carcinogenesis. Another protein belonging to gastroskine family GKN1 and GKN2 also have a protective role in gastric mucosa and downregulated in gastric cancer [75,76].

H. pylori induced Apoptosis

VacA toxin of *H. pylori*, MHC-II, Fas-FasL, transcription regulator NF-κβ of host were known for probably inducing apoptosis. *H. pylori* infection mediates insertion of VacA toxin into the mitochondrial membrane to induce and release cytochrome-C thereby activating Caspase 3 dependent cell-death signalling cascade which in turn activates mechanism of apoptosis [77-79]. Pathogen *H. pylori* binds or interacts to/with MHC-II on the surface of gastric epithelial cells to induce apoptosis [80]. *H. pylori* induce expression of Fas (cell-surface receptor) and FasL (Fas Ligand) and stimulate apoptosis [81]. Gastric epithelial cells respond to *H. pylori* by activating NF-κβ regulating inflammatory cascade (chemokines, iNOS) leading to apoptosis [82].

Concluding Remarks

Helicobacter pylori infection induces gastric inflammation, ulcer, and cancer. Bacterium colonizes in the acidic environment of the stomach. Chemoreceptor TlpB, in *H. pylori* senses pH and tends to move towards the less acidic region. The other mechanism that *H. pylori* uses is production of urease to neutralize its periplasm and cytoplasm. *H. pylori* then adhere to the epithelial cells with the help of adhesins such as BabA, SabA, AlpA, AlpB, HopZ, and OipA. Pathogen with help of toxin VacA, cytokines, gastrin then weakens the gastric mucosal barrier by loosening the mucous layer or disruption of mucous layer or by altering mucous glycoproteins to colonize in the mucous or submucous or epithelial cells. Cytotoxin associated gene pathogenicity island (cag PAI) codes for T4SS system that injects CagA, VacA and peptidoglycan into the host cell. Injection of CagA changes the expression of host genes, induces cell proliferation, loss of polarity and elongation of cell, degradation of cell-cell junctions, decrease in acid secretion and inflammation. Inflammatory cells produce cytokines such as MMPs, PGE2 and RONS, which in turn augment and prolong the inflammatory cascade. *H. pylori* is vulnerable to oxidative stress, acidity, peristalsis and phagocytes lethal leading to DNA damage in the genome. *H. pylori* uses the acquired transformation mediated recombination DNA repair for successful infection of the pathogen. Prolonged inflammation leads to ulcers by inducing G cells to secrete hormone gastrin, which in turn stimulates loads of acid damaging duodenum. Inflammatory mediators, NF-κβ, β-catenin signalling pathways induce indirectly or directly DSB, defective mitotic checkpoints, deregulating HR pathway of DSB repair and DNA repair enzymes leading to MSI and CI. MSI and CI induce genetic diversification randomly leading to activation of oncogenes and inactivation of tumor suppressor genes RUNX3, p53, ASPP2, TFF1, TFF2, TFF3, GK1 and GKN2.

Acknowledgements

DN, ACMP, CS and NNRR are thankful to the GITAM University, Visakhapatnam, India for providing the facility and support. NNRR and DN are thankful to University Grants Commission, New Delhi for the project funding [UGC Project F.No.42-636/2013 (SR) letter dated 25-03-2013]. DN is thankful for the Project Fellowship sponsored by UGC, New Delhi, India. The authors are also thankful to Prof. I. Bhaskar Reddy and Dr Malla Rama Rao for constant support throughout the research work. We profusely thank Dr D. Govinda Rao, GITAM University, Visakhapatnam, India for critical comments and reviewing of the manuscript.

References

- Blaser MJ (2005) An endangered species in the stomach. *Sci Am* 292: 38-45.
- Bizzozero G (1893) Ueber die schlauchförmigen Drüsen des Magendarmkanals und die Beziehungen ihres Epithels zu dem Oberflächenepithel der Schleimhaut". *Archiv für mikroskopische Anatomie* 42: 82-152.
- Konturek JW (2003) Discovery by Jaworski of *Helicobacter pylori* and its pathogenic role in peptic ulcer, gastritis and gastric cancer. *J Physiol Pharmacol* 54 Suppl 3: 23-41.
- Marshall BJ, Warren JR (1984) Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1: 1311-1315.
- Blaser MJ, Atherton JC (2004) *Helicobacter pylori* persistence: biology and disease. *J Clin Invest* 113: 321-333.

6. Salama NR, Hartung ML, Müller A (2013) Life in the human stomach: persistence strategies of the bacterial pathogen *Helicobacter pylori*. *Nat Rev Microbiol* 11: 385-399.
7. Blaser M (2011) Antibiotic overuse: Stop the killing of beneficial bacteria. *Nature* 476: 393-394.
8. Blaser MJ (2006) Who are we? Indigenous microbes and the ecology of human diseases. *EMBO Rep* 7: 956-960.
9. Blaser MJ, Chen Y, Reibman J (2008) Does *Helicobacter pylori* protect against asthma and allergy? *Gut* 57: 561-567.
10. Chen Y, Blaser MJ (2008) *Helicobacter pylori* colonization is inversely associated with childhood asthma. *J Infect Dis* 198: 553-560.
11. Linz B, Balloux F, Moodley Y, Manica A, Liu H, et al. (2007) An African origin for the intimate association between humans and *Helicobacter pylori*. *Nature* 445: 915-918.
12. Correa P, Piazuelo MB (2012) Evolutionary History of the *Helicobacter pylori* Genome: Implications for Gastric Carcinogenesis. *Gut Liver* 6: 21-28.
13. Pounder RE, Ng D (1995) The prevalence of *Helicobacter pylori* infection in different countries. *Aliment Pharmacol Ther* 9 Suppl 2: 33-39.
14. Smoak BL, Kelley PW, Taylor DN (1994) Seroprevalence of *Helicobacter pylori* infections in a cohort of US Army recruits. *Am J Epidemiol* 139: 513-519.
15. Everhart JE, Kruszon-Moran D, Perez-Perez GI, Tralka TS, McQuillan G (2000) Seroprevalence and ethnic differences in *Helicobacter pylori* infection among adults in the United States. *J Infect Dis* 181: 1359-1363.
16. Kusters JG, van Vliet AH, Kuipers EJ (2006) Pathogenesis of *Helicobacter pylori* infection. *Clin Microbiol Rev* 19: 449-490.
17. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, et al. (2014) Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* .
18. Pavithran K, Doval DC, Pandey KK (2002) Gastric cancer in India. *Gastric Cancer* 5: 240-243.
19. Stenström B, Mendis A, Marshall B (2008) *Helicobacter pylori*--the latest in diagnosis and treatment. *below Aust Fam Physician* 37: 608-612.
20. Logan RP, Walker MM (2001) ABC of the upper gastrointestinal tract: Epidemiology and diagnosis of *Helicobacter pylori* infection. *BMJ* 323: 920-922.
21. Rauws EA, Tytgat GN (1990) Cure of duodenal ulcer associated with eradication of *Helicobacter pylori*. *Lancet* 335: 1233-1235.
22. Graham DY, Lew GM, Evans DG, Evans DJ Jr, Klein PD (1991) Effect of triple therapy (antibiotics plus bismuth) on duodenal ulcer healing. A randomized controlled trial. *Ann Intern Med* 115: 266-269.
23. Perna F, Zullo A, Ricci C, Hassan C, Morini S, et al. (2007) Levofloxacin-based triple therapy for *Helicobacter pylori* re-treatment: role of bacterial resistance. *Dig Liver Dis* 39: 1001-1005.
24. Hsu PI, Wu DC, Chen A, Peng NJ, Tseng HH, et al. (2008) Quadruple rescue therapy for *Helicobacter pylori* infection after two treatment failures. *Eur J Clin Invest* 38: 404-409.
25. Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon AT, et al. (2012) Management of *Helicobacter pylori* infection--the Maastricht IV/ Florence Consensus Report. *Gut* 61: 646-664.
26. Fischbach L, Evans EL (2007) Meta-analysis: the effect of antibiotic resistance status on the efficacy of triple and quadruple first-line therapies for *Helicobacter pylori*. *Aliment Pharmacol Ther* 26: 343-357.
27. Graham DY, Shiotani A (2008) New concepts of resistance in the treatment of *Helicobacter pylori* infections. *Nat Clin Pract Gastroenterol Hepatol* 5: 321-331.
28. Neelapu NR, Pavani T (2013) Identification of novel drug targets in HpB38, HpP12, HpG27, Hpshi470, HpSJM180 strains of *Helicobacter pylori* : an in silico approach for therapeutic intervention. *Curr Drug Targets* 14: 601-611.
29. Neelapu NR, Srimath-Tirumala-Peddinti RC, Nammi D, Pasupuleti AC (2013) New strategies and paradigm for drug target discovery: a special focus on infectious diseases tuberculosis, malaria, leishmaniasis, trypanosomiasis and gastritis. *Infect Disord Drug Targets* 13: 352-364.
30. Selgrad M, Malfertheiner P (2008) New strategies for *Helicobacter pylori* eradication. *Curr Opin Pharmacol* 8: 593-597.
31. Lowenthal AC, Simon C, Fair AS, Mehmood K, Terry K, et al. (2009) A fixed-time diffusion analysis method determines that the three cheV genes of *Helicobacter pylori* differentially affect motility. *Microbiology* 155: 1181-1191.
32. Rader BA, Wreden C, Hicks KG, Sweeney EG, Ottemann KM, et al. (2011) *Helicobacter pylori* perceives the quorum-sensing molecule AI-2 as a chemorepellent via the chemoreceptor TlpB. *Microbiology* 157: 2445-2455.
33. Goers Sweeney E, Henderson JN, Goers J, Wreden C, Hicks KG, et al. (2012) Structure and proposed mechanism for the pH-sensing *Helicobacter pylori* chemoreceptor TlpB. *Structure* 20: 1177-1188.
34. Ferrero RL, Labigne A (1993) Cloning, expression and sequencing of *Helicobacter felis* urease genes. *Mol Microbiol* 9: 323-333.
35. Park IS, Hausinger RP (1995) Evidence for the presence of urease apoprotein complexes containing UreD, UreF, and UreG in cells that are competent for in vivo enzyme activation. *J Bacteriol* 177: 1947-1951.
36. Rektorschek M, Buhmann A, Weeks D, Schwan D, Bensch KW, et al. (2000) Acid resistance of *Helicobacter pylori* depends on the UreI membrane protein and an inner membrane proton barrier. *Mol Microbiol* 36: 141-152.
37. Wen Y, Marcus EA, Matrubutham U, Gleeson MA, Scott DR, et al. (2003) Acid-adaptive genes of *Helicobacter pylori*. *Infect Immun* 71: 5921-5939.
38. Mollenhauer-Rektorschek M, Hanauer G, Sachs G, Melchers K (2002) Expression of UreI is required for intragastric transit and colonization of gerbil gastric mucosa by *Helicobacter pylori*. *Res Microbiol* 153: 659-666.
39. Burrows CF (2010) The gastric mucosal barrier: Why the stomach does not digest itself. In: *Mechanisms of Disease in Small Animal Surgery*. M. Joseph Bojrab, Eric Monnet (Eds.) 3rd Edition, Teton New Media Inc., USA.
40. Petersen AM, Krogfelt KA (2003) *Helicobacter pylori*: an invading microorganism? A review. *FEMS Immunol Med Microbiol* 36: 117-126.
41. Ilver D, Arnqvist A, Ogren J, Frick IM, Kersulyte D, et al. (1998) *Helicobacter pylori* adhesin binding fucosylated histo-blood group antigens revealed by retagging. *Science* 279: 373-377.
42. Mahdavi J, Sondén B, Hurtig M, Olfat FO, Forsberg L, et al. (2002) *Helicobacter pylori* SabA adhesin in persistent infection and chronic inflammation. *Science* 297: 573-578.
43. Moodley Y, Linz B, Yamaoka Y, Windsor HM, Breurec S, et al. (2009) The peopling of the Pacific from a bacterial perspective. *Science* 323: 527-530.
44. Yamaoka Y (2010) Mechanisms of disease: *Helicobacter pylori* virulence factors. *Nat Rev Gastroenterol Hepatol* 7: 629-641.
45. Tegtmeyer N, Wessler S, Backert S (2011) Role of the cag-pathogenicity island encoded type IV secretion system in *Helicobacter pylori* pathogenesis. *FEBS J* 278: 1190-1202.
46. Hatakeyama M (2008) SagA of CagA in *Helicobacter pylori* pathogenesis. *Curr Opin Microbiol* 11: 30-37.
47. O'Connor PM, Lapointe TK, Jackson S, Beck PL, Jones NL, et al. (2011) *Helicobacter pylori* activates calpain via toll-like receptor 2 to disrupt adherens junctions in human gastric epithelial cells. *Infect Immun* 79: 3887-3894.
48. Beales IL, Calam J (1997) *Helicobacter pylori* stimulates granulocyte-macrophage colony-stimulating factor (GM-CSF) production from cultured antral biopsies and a human gastric epithelial cell line. *Eur J Gastroenterol Hepatol* 9: 451-455.
49. Cho SO, Lim JW, Kim KH, Kim H (2010) Involvement of Ras and AP-1 in *Helicobacter pylori*-induced expression of COX-2 and iNOS in gastric epithelial AGS cells. *Dig Dis Sci* 55: 988-996.
50. Cavallo P, Cianciulli A, Mitolo V, Panaro MA (2011) Lipopolysaccharide (LPS) of *Helicobacter pylori* modulates cellular DNA repair systems in intestinal cells. *Clin Exp Med* 11: 171-179.

51. Gobert AP, Asim M, Piazuolo MB, Verriere T, Scull BP, et al. (2011) Disruption of nitric oxide signaling by *Helicobacter pylori* results in enhanced inflammation by inhibition of heme oxygenase-1. *J Immunol* 187: 5370-5379.
52. D'Elios MM, Amedei A, Cappon A, Del Prete G, de Bernard M (2007) The neutrophil-activating protein of *Helicobacter pylori* (HP-NAP) as an immune modulating agent. *FEMS Immunol Med Microbiol* 50: 157-164.
53. Huang XW, Luo RH, Zhao Q, Shen ZZ, Huang LL, et al. (2011) *Helicobacter pylori* induces mitochondrial DNA mutation and reactive oxygen species level in AGS cells. *Int J Med Sci* 8: 56-67.
54. Peek RM Jr, Crabtree JE (2006) *Helicobacter* infection and gastric neoplasia. *J Pathol* 208: 233-248.
55. Amieva MR, El-Omar EM (2008) Host-bacterial interactions in *Helicobacter pylori* infection. *Gastroenterology* 134: 306-323.
56. Atherton JC, Blaser MJ (2009) Coadaptation of *Helicobacter pylori* and humans: ancient history, modern implications. *J Clin Invest* 119: 2475-2487.
57. Evans DJ Jr, Evans DG, Takemura T, Nakano H, Lampert HC, et al. (1995) Characterization of a *Helicobacter pylori* neutrophil-activating protein. *Infect Immun* 63: 2213-2220.
58. Polenghi A, Bossi F, Fischetti F, Durigutto P, Cabrelle A, et al. (2007) The neutrophil-activating protein of *Helicobacter pylori* crosses endothelia to promote neutrophil adhesion in vivo. *J Immunol* 178: 1312-1320.
59. Olczak AA, Olson JW, Maier RJ (2002) Oxidative-stress resistance mutants of *Helicobacter pylori*. *J Bacteriol* 184: 3186-3193.
60. O'Rourke EJ, Chevalier C, Pinto AV, Thiberge JM, Ielpi L, et al. (2003) Pathogen DNA as target for host-generated oxidative stress: role for repair of bacterial DNA damage in *Helicobacter pylori* colonization. *Proc Natl Acad Sci U S A* 100: 2789-2794.
61. Michod RE, Bernstein H, Nedelcu AM (2008) Adaptive value of sex in microbial pathogens. *Infect Genet Evol* 8: 267-285.
62. Dorer MS, Fero J, Salama NR (2010) DNA damage triggers genetic exchange in *Helicobacter pylori*. *PLoS Pathog* 6: e1001026.
63. Loughlin MF, Barnard FM, Jenkins D, Sharples GJ, Jenks PJ, et al. (2003) *Helicobacter pylori* mutants defective in RuvC Holliday junction resolvase display reduced macrophage survival and spontaneous clearance from the murine gastric mucosa. *Infect Immun* 71: 2022-2031.
64. Wang G, Maier RJ (2008) Critical role of RecN in recombinational DNA repair and survival of *Helicobacter pylori*. *Infect Immun* 76: 153-160.
65. Schubert ML, Peura DA (2008) Control of gastric acid secretion in health and disease. *Gastroenterology* 134: 1842-1860.
66. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A (2009) Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis* 30: 1073-1081.
67. Hayden MS, Ghosh S (2008) Shared principles in NF-kappaB signaling. *Cell* 132: 344-362.
68. Yang XD, Huang B, Li M, Lamb A, Kelleher NL, et al. (2009) Negative regulation of NF-kappaB action by Set9-mediated lysine methylation of the RelA subunit. *EMBO J* 28: 1055-1066.
69. Murata-Kamiya N, Kurashima Y, Teishikata Y, Yamahashi Y, Saito Y, et al. (2007) *Helicobacter pylori* CagA interacts with E-cadherin and deregulates the beta-catenin signal that promotes intestinal transdifferentiation in gastric epithelial cells. *Oncogene* 26: 4617-4626.
70. Uefuji K, Ichikura T, Mochizuki H (2000) Cyclooxygenase-2 expression is related to prostaglandin biosynthesis and angiogenesis in human gastric cancer. *Clin Cancer Res* 6: 135-138.
71. Tsang YH, Lamb A, Romero-Gallo J, Huang B, Ito K, et al. (2010) *Helicobacter pylori* CagA targets gastric tumor suppressor RUNX3 for proteasome-mediated degradation. *Oncogene* 29: 5643-5650.
72. Tsang YH, Lamb A, Chen LF (2011) New insights into the inactivation of gastric tumor suppressor RUNX3: the role of *H. pylori* infection. *J Cell Biochem* 112: 381-386.
73. Kitajima Y, Ohtaka K, Mitsuno M, Tanaka M, Sato S, et al. (2008) *Helicobacter pylori* infection is an independent risk factor for Runx3 methylation in gastric cancer. *Oncol Rep* 19: 197-202.
74. Buti L, Spooner E, Van der Veen AG, Rappuoli R, Covacci A, et al. (2011) *Helicobacter pylori* cytotoxin-associated gene A (CagA) subverts the apoptosis-stimulating protein of p53 (ASPP2) tumor suppressor pathway of the host. *Proc Natl Acad Sci U S A* 108: 9238-9243.
75. Toback FG, Walsh-Reitz MM, Musch MW, Chang EB, Del Valle J, et al. (2003) Peptide fragments of AMP-18, a novel secreted gastric antrum mucosal protein, are mitogenic and motogenic. *Am J Physiol Gastrointest Liver Physiol* 285: G344-G353.
76. Walsh-Reitz MM, Huang EF, Musch MW, Chang EB, Martin TE, et al. (2005) AMP-18 protects barrier function of colonic epithelial cells: role of tight junction proteins. *Am J Physiol Gastrointest Liver Physiol* 289: G163-G171.
77. Jones NL, Shannon PT, Cutz E, Yeger H, Sherman PM (1997) Increase in proliferation and apoptosis of gastric epithelial cells early in the natural history of *Helicobacter pylori* infection. *Am J Pathol* 151: 1695-1703.
78. Rudi J, Kuck D, Strand S, von Herbay A, Mariani SM, et al. (1998) Involvement of the CD95 (APO-1/Fas) receptor and ligand system in *Helicobacter pylori*-induced gastric epithelial apoptosis. *J Clin Invest* 102: 1506-1514.
79. Lancellotti M, Brocchi M, da Silveira WD (2006) Bacteria-induced apoptosis: an approach to bacterial pathogenesis. *Braz J morphol Sci* 23: 75-86.
80. Fan X, Gunasena H, Cheng Z, Espejo R, Crowe SE, et al. (2000) *Helicobacter pylori* urease binds to class II MHC on gastric epithelial cells and induces their apoptosis. *J Immunol* 165: 1918-1924.
81. Caulfield AJ, Lathem WW (2014) Disruption of fas-fas ligand signaling, apoptosis, and innate immunity by bacterial pathogens. *PLoS Pathog* 10: e1004252.
82. Tak PP, Firestein GS (2001) NF-kappaB: a key role in inflammatory diseases. *J Clin Invest* 107: 7-11.