Review

40 Years of *Helicobacter pylori*: A Revolution in Biomedical Thought

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Abstract: *Background:* Various microorganisms such as bacteria, virus, and fungi can infect humans and cause not just a simple infection but septic conditions, organ dysfunction, and precancerous conditions or cancer involving various organ systems. After the discovery of the microscope, it was easier to discover and study such microorganisms, as in the case of *Helicobacter pylori*, a pathogen that was seen in the distant era of the nineteenth century but without being recognized as such. It took 100 years to later discover the pathogenesis and the cancer that this bacterium can cause. Since it was discovered, until today, there has been a continuous search for the understanding of its pathogenetic mechanisms, and the therapeutic approach is continuously updated. *Methods:* We investigated how diagnosis and therapy were dealt with in the past and how researchers sought to understand, exactly, the pathogenetic biomolecular mechanisms of *H. pylori*, from the genesis of the infection to the current knowledge, with an analysis of carcinogenic mechanisms in the stomach. We have examined the scientific evolution of the knowledge of the disease over these 40 years in the gastroenterological and pharmacological fields. This was possible through a search in the databases of Medline, the WHO website, the Centers for Disease Control and Prevention (CDC) website, PubMed, and Web of Science to analyze the earlier and the latest data regarding *H. pylori*. *Results:* With the scientific discoveries over time, thanks to an increasing number of progressions in scientific research in the analysis of the gastric mucosa, the role of *Helicobacter pylori* in peptic ulcer, carcinogenesis, and in some forms of gastric lymphoma was revealed. Furthermore, over the years, the biomolecular mechanism involvement in some diseases has also been noted (such as cardiovascular ones), which could affect patients positive for *H. pylori*. *Conclusions:* Thanks to scientific and technological advances, the role of the bacterium *H. pylori* in carcinogenesis has been discovered and demonstrated, and new prospective research is currently attempting to investigate the role of other factors in the stomach and other organs. Cancer from *H. pylori* infection had a high incidence rate compared to various types of cancer, but in recent years, it is improving thanks to the techniques developed in the detection of the bacterium and the evolution of therapies. Thus, although it has become an increasingly treatable disease, there is still continuous ongoing research in the field of treatment for resistance and pharma compliance. Furthermore, in this field, probiotic therapy is considered a valid adjuvant.

Keywords: *Helicobacter pylori*; history of medicine; gastric cancer; carcinogenesis; seroprevalence; antimicrobials; chemotherapy; microbiota; probiotics

1. Introduction

Helicobacter pylori is a Gram-negative bacterium, microaerophilic (requires O_2 at a lower concentration than in the atmosphere: 5% O_2, 15% CO_2, and 80% N), has a helical shape, and is categorized as a curved rod not spirochaete bacterium (3 µm long, diameter about 0.5 µm) that usually colonizes the gastric mucosa [1]. It has the ability to transform

from bacillary to coccoid form (a survival form) [2] and can form organized bacterial surface colonies (bio-membranes). In its spiral form, it can survive for at least a week in water, and in the coccoid form, probably for much longer periods. The outer layer of the membrane is made up of phospholipids and lipopolysaccharides (LPS) but also cholesterol glycosides (which are present in a few other Gram-negative bacteria). Is highly motile thanks to the presence of flagella (four to six flagella at the same location) as with all the *Helicobacter* spp. (gastric and enterohepatic ones), composed of two copolymerized flagellins, FlaA and FlaB [3,4]. It contains a hydrogenase that uses H_2 from intestinal bacteria by oxidizing it for energy and also produces oxidase, catalase, and urease. *H. pylori* consists of a wide diversity of strains and genomes that have been completely sequenced. *H. pylori* strain 26,695 has a circular genome of approximatively 1.7 million base pairs and 1590 genes. Studies on the genome have been necessary to understand the pathogenetic mechanisms, or its ability to cause diseases [5–7].

H. pylori infection is extremely common and is thought to affect more than 50% of the world population. The annual incidence rate of *H. pylori* differs significantly between developed and developing countries, with this difference mainly affecting childhood. Later in adulthood, the annual rate of infection increases for developing countries and decreases in developed countries due to socioeconomic conditions. Transmission is via fecal–oral, oral–oral (dental), gastro–oral, and sexual behavior routes [8]. *H. pylori* can be detected in dental plaque (oral biofilms) and from the feces of infected adults both by culture and biomolecular techniques (PCR). The infection appears to be acquired throughout life, mainly starting in infancy [9]. Interfamilial transmission is responsible for the higher incidence of infections in parents and siblings of *H. pylori*-positive children and children of *H. pylori*-positive parents [10,11]. The isolation of *H. pylori* strains of the same genotype in mothers and their offspring—sometimes different genotypes from that of fathers—highlights the role of close contact [12,13]. This study seeks to analyze all the knowledge of the biomolecular mechanisms, diagnosis, and treatment of infection to date through a historical scientific path. Of particular interest is the association of *H. pylori* infection with extra-digestive diseases.

2. Materials and Methods

A search of manuscripts was carried out in large databases from 1981 until present. From the results, the most innovative ones of each period concerning the history of the discovery, the epidemiology, and the physiopathology of carcinogenesis of *H. pylori* infection were chosen.

2.1. Historical Helicobacter pylori *Traces*

Since the time of ancient Egypt (Ebers Papyrus, 1600 BC), and later in the classical world with Hippocrates, Galen, Dioscurides, and others, gastrointestinal symptoms were described and various remedies, e.g., extracts from specific herbs, were used to treat various gastric symptoms (such as *Elettaria cardamomum* for indigestion and flatulence) or antidotes such as *Theriaca* for gastrointestinal or other poisoning [14–16].

Later, at the end of the sixteenth century, a separate invention was the beginning to forever change the study of organisms. In 1595, the Dutch pair Hans and Zacharias Janssen (father and son) built the first microscope to enlarge an image 20 times. Thereafter, in 1674, Anthony van Leeuwenhoek (1632–1723), a naturalist and optician, created his microscope and magnified objects 300 times (Figure 1) [17,18]. Furthermore, he made important biological discoveries such as red blood cells, numerous bacteria and protozoa (describing, with a good precision, *Volvox, Vorticella, Opaline, Nyctotherus, Trichomonas vaginalis, Bacterium coli, Azotobacter, Amylobacter saccarobutyricum,* and others). He was the first person to see microorganisms, which he called small "insects" (animalcules). In fact, he noticed a sample of his teeth and this was the first time that bacteria were observed. Van Leeuwenhoek noted: "There are smaller bugs in a man's toothpick than there are in an

entire kingdom". It soon became clear that the creatures discovered by Leeuwenhoek not only live in the world around them, but also have a significant impact on it [18].
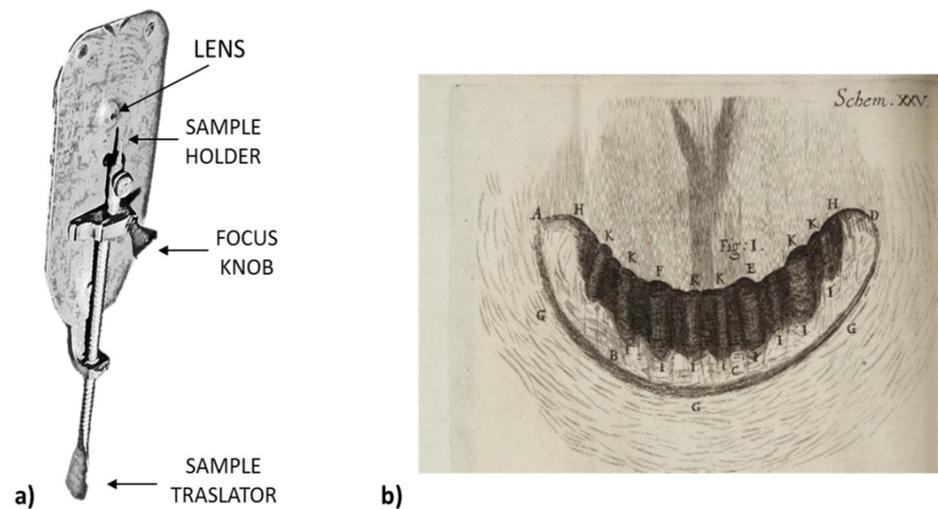
Figure 1. (**a**) Anthony van Leeuwenhoek's microscope; (**b**) Robert Hooke's observations under his microscope: teeth of the snail description (from his book "Micrographia", p. 180, schem. XXV, fig.1, National Library of Wales, UK).

At the same time, the English scientist Robert Hooke (1635–1703) built his microscope that could enhance 500 times and observed thin sections of cork containing many "cells", a term we still use today for the life unit. They discovered that they are also responsible for human and animal diseases, and the most contagious historical epidemic infections such as plague of cholera, syphilis, and others. In the following years, microscopes continuously evolved, and today, we have optical microscopes and also powerful electronic microscopes that allow us to see the structures of microorganisms, including viruses, because the magnification is more than 300,000 times [18,19].

The study of bacteria of the gastric mucosa by microscope began from 1875 onwards, when G. Bottcher and M. Letulle demonstrated the presence of bacteria in the margins of ulcers (Table 1) [20,21]. Subsequently, in 1892, the Italian scientist G. Bizzozero was one of the pioneers of histology and of the use of the microscope in medical research. He identified spirochetes (spiral bacteria) in the gastric mucosa of dogs, thus demonstrating that some bacteria can survive in the acidic environment of the stomach (Figure 2) [20,22–25]. Later, the term peptic ulcer or peptic ulcer disease (PUD) was used for the first time in 1882 by Heinrich Irenaeus Quincke, emphasizing that gastric juice is responsible for gastric ulcers compared to the previous hypothesis that pepsin is responsible (digestion theory). In the first 10 years after its discovery in 1981, it was proven that *H. pylori* accounts for 80% of peptic ulcers, even though scientists for years ignored the possibility that it was due to a germ [20,21,23].

Table 1. The main steps in the research for bacteria in the stomach over time (Adapted from Suzuki, H.; Warren, R.; Marshall, B. *Helicobacter pylori*; Springer: Berlin/Heidelberg, Germany, 2016, p. 8).

Gastric Bacteria Discoveries—Historical Timeline	
Year	**Researchers**
1875	G. Bottcher/M. Letulle (demonstrated bacteria in ulcer margins)
1881	C. Klebs (indentified bacterial colonization and inter-glandular small cell infiltration)
1889	W. Jaworski (noticed spiral organisms, *Vibrio rugula,* in gastric washings)
1893	G. Bizzozero (identified spirochetes in gastric mucosa of dogs)

Table 1. *Cont.*

Gastric Bacteria Discoveries—Historical Timeline	
Year	**Researchers**
1896	H. Salomon (spirochetes noted in gastric mucosa and experimentally transferred to mice)
1906	W.Krienitz (noticed spirochetes in gastric contents of a patient with gastric carcinoma)
1916	E.C. Rosenow (described *Streptococcus*-induced gastric ulcers)
1917	L.R. Dragstedt (bacteria in experimental ulcers, no significant role identified)
1924	J.M. Luck (discovered gastric mucosal urease-1 in dogs)
1925	B. Hoffma (described *B. hoffmani* as a putative ulcerous agent)
1938	J.L. Doenge (*Spirochetes* in gastric glands of *Macacus rhesus* and humans)
1940	S.Freedberg (note spirochaetes in biopsies of patients operated on for ulcer or stomach cancer) and F.D. Gorham (postulated gastric acidophilic bacteria as etiologic agents in ulcer disease)
1983	J.R. Warren (identified *Campylobacter pylori* in human gastritis)
1967	S.Ito (in his "Handbook of physiology" reported an image of a spiral bacterium with flagella such as the *Helicobacter pylori* from samples taken from own stomach)
1981	R.Warren (after biopsy noticed curved bacteria in the stomach of some patients) and B.Marshall (begins the pilot study for this)
1982	B. Marshall (isolated and cultured *Helicobacter pylori*)
1983	B. Marshall and R. Warren (they describe *H. pylori* as a new species on Lancet)
1985/1987	B. Marshall/A. Morris (ingested and proved the infectivity of *H. pylori* according to the Koch's 3rd criterium postulate)
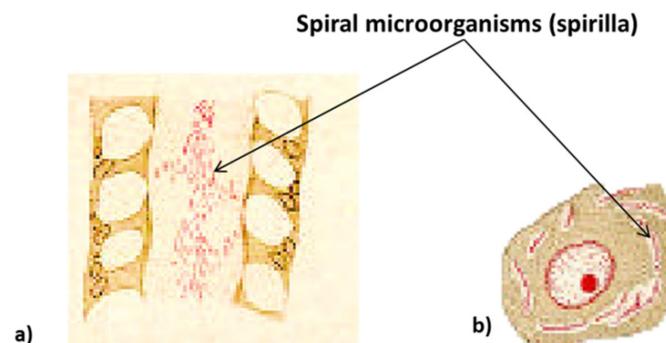
Figure 2. Partial illustrations: (**a**) the spiral microorganisms (c-spirilla) in the mucus layer and gastric gland, drawn by the Italian *Helicobacter* pioneer G. Bizzozero, the first that detected *Helicobacter* spp. by observing the stomachs of dogs and cats with a microscope (1893). Later, in 1996, the renaming of *Helicobacter heilmannii* in *Helicobacter bizzozeronii* reports his last name; (**b**) spiral microorganisms in the protoplasm, drawn by H. Salomon (1896) [25].

In 1906, the first medical report on the presence of spirochetes in the gastric contents of patients with human target spiral gastric carcinoma bacteria was published by W. Krienitz. Later, in the 1920s, the urease enzyme was discovered in the gastric mucosa of primates. In the 1930s, the first necropsy study on gastric tissue samples in patients that died with gastric carcinoma was performed in the United States, which had a high incidence rate at that time. In the analyzed samples, the presence of "spirochetes" bacteria was observed in 43% of the samples [20,21,23]. Subsequently, the evolution of endoscopic techniques allowed to obtain a more accurate observation of gastric sites where colonies of Gram-negative bacteria were identified, especially in patients with gastric pathologies [21,23]. In 1981 began the first trial by Robin Warren of patients selected by Barry Marshall. Subsequently, in 1983, the culture of spiral microbes from gastric mucosal biopsies from patients with chronic active gastritis was announced for the first time. Indeed, the researchers Robin

Warren and Barry Marshall performed the culture and isolation of spiral bacteria in 58 gastric biopsies, which were named *Campylobacter pyloridis*, because the bacterium had the morphological characteristics of the *Campylobacter* genus. This is due to the similar biological characteristics and the similar guanine/cytosine ratio (G+C ratio: 30–48% molar) in *Campylobacter* spp. [24–26]. Experimental evidence of the role of *H. pylori* in causing gastric damage was subsequently confirmed by the fulfillment of Koch's criteria for pathogenic microorganisms by B. Marshall [27]. Through the ingestion of *H. pylori* from a patient with gastritis, as a result, he became sick himself. The two Australian researchers, Marshall and Warren, were the first to carry out the cultivation. Subsequently, in 1987, it was decided to rename the bacterium *Campylobacter pylori*. Additionally, it was the first demonstration of a relationship between *H. pylori* and gastric damage, and in the same year, the foundation of the European *H. pylori* Study Group (EHSG) was created. However, in 1989, after the morphological and genetic identification of this microorganism showed that it could not be considered a member of the *Campylobacter* genus, the name *Helicobacter pylori* prevailed, a name that is still used internationally [8,28–32]. The need to identify the new genus *Helicobacter* was indicated by the sequences of *Campylobacter jejuni* and *H. pylori*, the results of an extensive analysis of DNA–DNA hybridization experiments, the sequence of rRNA genes 16S and 23S, the fatty acid profile of membranous phospholipids and respiratory mitochondrial chain components [33–35], Meanwhile, since 1990 and until 2000, many other *Helicobacter* spp. have been discovered such as those of *H. felis*, *H. bilis*, and others [36]. Subsequently, the etiological association of *H. pylori* infection and its correlation with gastric pathologies such as gastritis, gastroduodenal ulcer, gastric cancer, and, finally, mucosa-associated lymphoid tissue (MALT) lymphoma (MALToma) radically changed the treatment of gastric pathologies. The discovery was so important that it was recognized by the International Medical Community, which awarded Marshall and Warren with the Nobel Prizes for Medicine in 2005 [21,36–38].

The time period during which *H. pylori* colonized the human stomach remains unknown, but the phylogenetic characteristics of the different geographic populations of *H. pylori* reflect significant events in human prehistory. Studies have shown that thanks to the migration of populations, the bacterium migrated from the African continent to the rest of the world about 58,000 years ago and has been estimated to have colonized humans before 115,000 years (Figure 3) [39,40]. Phylogenetic comparisons showed a similar evolution in humans and *H. pylori* and that the bacterium's natural host is humans. Therefore, zoonotic transmission is not possible, despite sporadic isolation of gastric strains of *H. pylori* in some mammals such as felines, monkeys, and others [41].
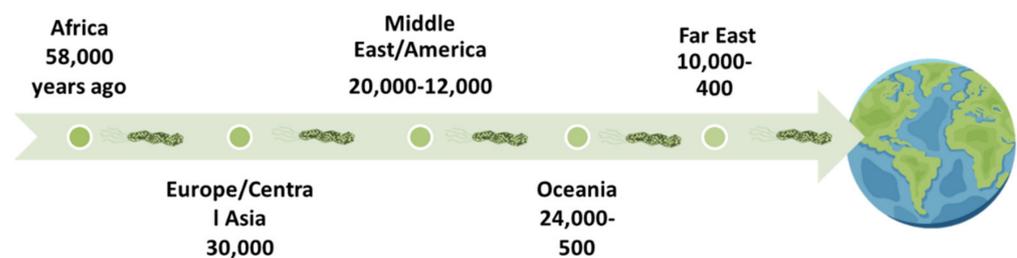
Figure 3. The spread of *H. pylori* in the continents over time.

2.2. The Biomolecular Knowledge Developments

H. pylori, in order to finally exert its pathogenic action, must firstly survive in the acidic gastric environment and penetrate the protective barrier of the gastric mucosa to eventually colonize the gastric mucosa (Table 2). Subsequently, to multiply inside the mucosa, it must escape the host's immune defense mechanisms [42].

Table 2. The actions of the virulence factors of *H. pylori.*

Virulence Factors in *H. pylori*							
Flagella	Urease	Lipopolysaccharides	Adhesins	Type IV Secretion System	Exotoxins	Lytic Enzymes	Heat Shock Proteins (Hsps)
Chemotaxis	Buffer the gastric acidic pH (creates mucosal damage through ammonia production)	Cell adhesion andinflammation	Cell adhesion, inflammation, stimulates the increase of sialyl-Lewis x antigen on the gastric mucosa.	Inject CagA and other factors. It causes the production of pro-inflammatory factors with subsequent cell apoptosis	VacA causes mucosal damage	Mucinases, proteases, lipases that cause damage to the mucosa	HSP-A and HSP-B proteins lead to inflammation

H. pylori possesses five major families of outer membrane proteins (OMPs) [24] such as adhesins, porins, iron transporters, flagellar proteins, and other proteins with unknown function [43]. Thus, the virulence factors to achieve this are divided into two categories. The first includes the factors necessary for the initial colonization of the gastric mucosa, common to all *H. pylori* strains (except for some mutant strains). The second includes flagella, adhesins (BabA/B, SabA, AlpA/B, OipA, and HopZ), and urease. The flagellum has a spiral shape which allows it to move from the gastric lumen (where the pH is acidic) deep into the mucus, where the pH is almost neutral, and allows it to grow and multiply (Figure 4) [44,45].
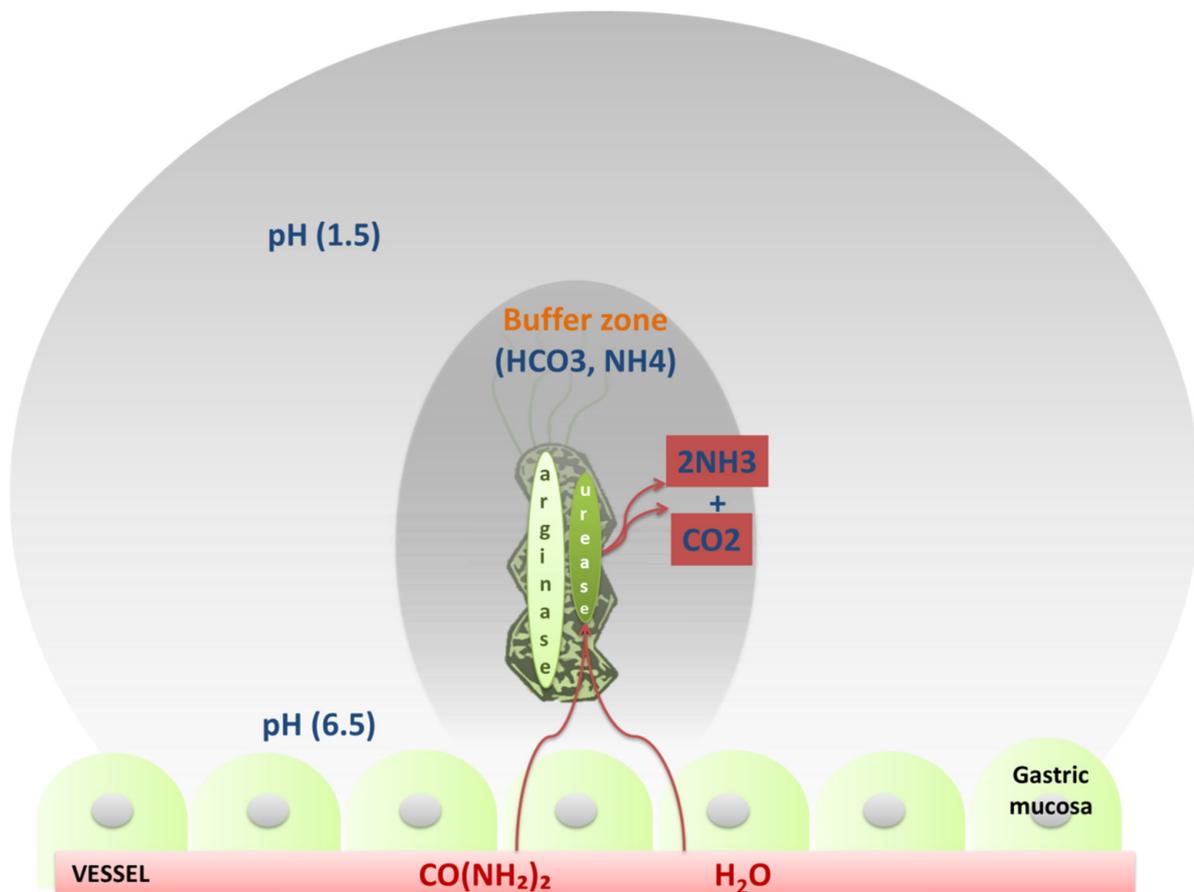
Figure 4. *H. pylori* has the ability to detect the pH level of the stomach environment and, thanks to its flagella, to go to the region with the least acidic pH (chemotaxis). *H. pylori* moves rapidly with the help of its flagella ending in a swollen extremity, consisting of two structural subunits, FlaA and FlaB, and a hook (FlgE) [46]. Other flagella proteins include the

flagellar biosynthetic protein FliP (FliP), which influences mobility through slipped-strand mispairing-mediated frameshifting of DNA. In addition, they have a distinctive shell, made up of the HpaA protein, which protects the bacterium from the harmful effects of stomach acid [47]. It also neutralizes the strong pH by promoting a rich production of urease (it can be located on the surface and inside the bacterium). The bacterium accumulates $CO(NH_2)_3$ and H_2O from the vessels and from the stomach itself, and the enzyme converts them by chemical reaction in $2NH_3$ and CO_2 which neutralize gastric acid, creating a buffer barrier around the *H. pylori*, surrounding the bacteria to protect them from strong acids in the environment. This also makes urease necessary to maintain a chronic infection. In addition, the *H. pylori* arginase enzyme captures the L-arginine reaction to produce L-ornithine and $CO(NH_2)_3$. This helps in adaptation and resistance to the acidic environment of the stomach and for the colonization of the bacterium towards the epithelium. Furthermore, the subsequent conversion of L-ornithine in polyamines contributes to the dysregulation of the host's immune response to infection [48].

Adhesins are proteins which are considered essential for the stable adhesion of *H. pylori* to gastric epithelial cells (Figure 5) Finally, the production of urease was initially thought to be a necessary factor for the infection, needed in large amounts [48,49]. In fact it was demonstrated through a complete transcription analysis using differential RNA-seq, which confirmed the main virulence loci such as the urease operongene cluster *ureABIEFGH* and the pathogenicity island of the cag. In addition, *H. pylori* arginase has a role in allowing the bacterium to not be recognized from the immune system by competing with nitric oxide (NO) synthase for L-arginine, thereby reducing NO production. However, NO is not only an antimicrobial agent but also a useful component of innate immunity [48,50].
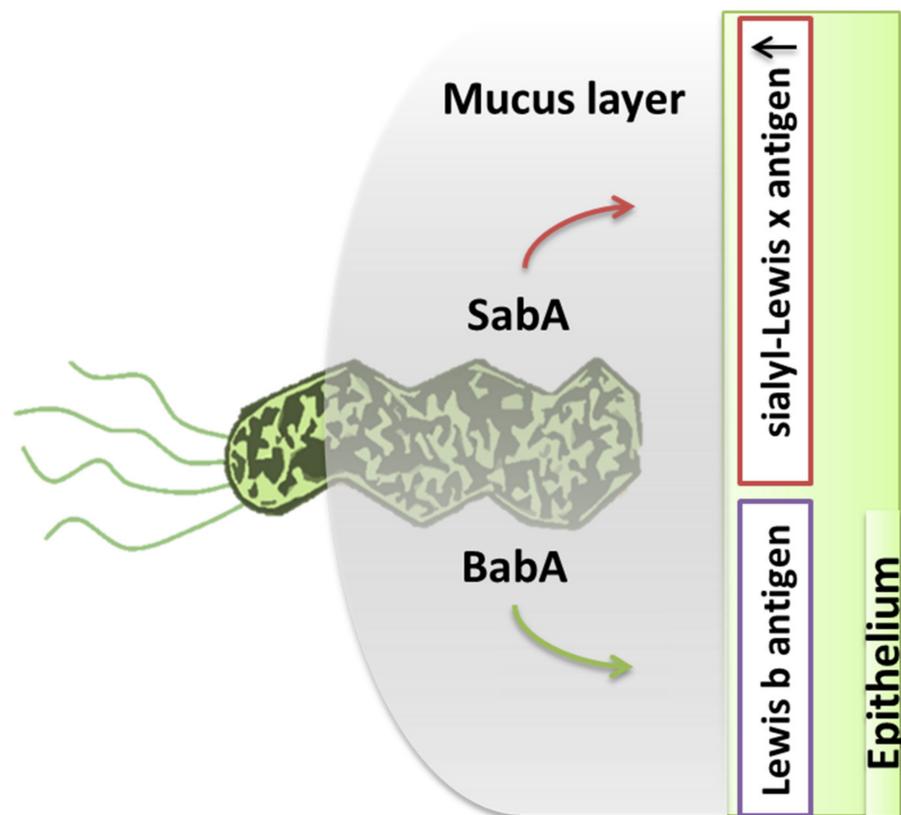
Figure 5. *H. pylori* adheres to the lipids and carbohydrates of the stomach epithelium through the production of adhesins. The adhesin BabA will bind with the Lewis b antigen of the epithelial cell. Another adhesin, SabA, binds with the epithelial cell and stimulates the increase in sialyl-Lewis x antigen on the gastric mucosa. The bacterium is usually found in the mucus area or on the epithelial cells, but rarely within them [50–52].

The second group of virulence factors is not considered necessary for initial colonization and consists of polysaccharidases, adhesion protein bab A2, cip A proteins (encoded by the *HPO 638* gene), Heat shock HspA and HspB proteins (*hspA* and *hspB* heat-shock gene cluster), exotoxins such as vacuolating cytotoxin A (VacA), and lytic enzymes (mucinases, proteases, and lipases) that cause damage to the mucosa [53]. The infection, therefore, promotes a greater production of cytokines by itself (interleukins and tumor necrosis factor-α (TNF-α)), which has a negative effect on the cells and the whole organism. The toxigenic gene vacuolating cytotoxin autotransporter (*vacA Q48245*) and its subtypes s1/m1 and s1/m2 promote disruption of the calcium channel TRPML1, thus increasing the risk for the development of gastric carcinoma. [54] However, among the virulence agents of *H. pylori* is the antigenic protein cytotoxin-associated protein A (CagA, molecular weight 125–140 kDa). CagA is an immunomodulatory extracellular protein of some strains of *H. pylori* (Figure 6) [55,56].
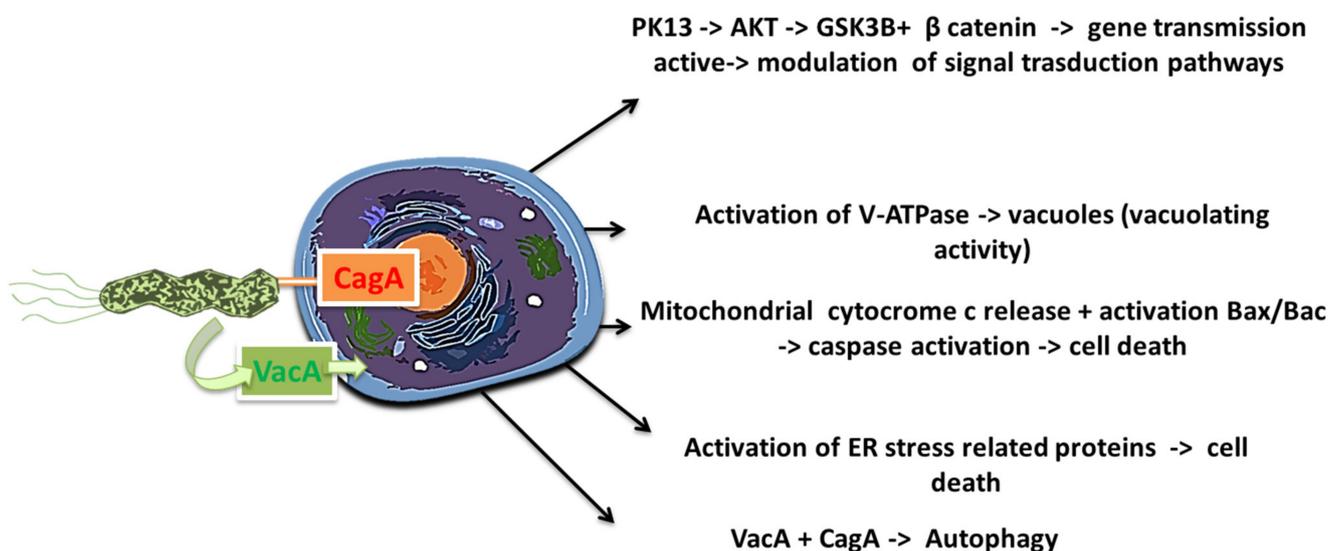
Figure 6. The toxigenic gene vacuolating cytotoxin A (*vacA*) and the synergy with cytotoxin-associated protein A (*CagA*) (released by the type IV secretory system—T4SS) effects on the cell.

After 1997, the cag region of microbial DNA was identified, which was designated as cag pathogenicity island—cag-PAI (dimension ~40 kbp, composed by ~30 genes). It is considered the main virulence factor of *H. pylori* [57]. Some researchers compared this region of pathogenicity to those found in uropathogenic strains of *Escherichia coli*. Considering this and the presence of a low GC content in cag-PAI, we can hypothesize that cag-PAI was probably acquired by horizontal transfer from another bacterial species such as *E. coli* [58–60]. The cag-PAI region is responsible for encoding the CagA protein as well as for the transfer of this protein and possibly other *Helicobacter* proteins from the bacterium to the cytoplasm of the epithelial cells of the gastric mucosa (Figure 7) [60–62]. Upon entering the epithelial cell, the CagA protein is phosphorylated by modifying the action of many intracellular enzyme systems such as that of the SHP-2(protein tyrosine phosphatase) system [63]. This action will lead to the activation of apoptotic mechanisms, interruption of the normal cell proliferation of the gastric epithelium and promoting a more intense inflammatory response from the host [64,65]. In fact, the strains of CagA(+) *H. pylori* have a high infectious power, determined by both the high anti-inflammatory response and the dysregulation of the proliferative system of gastric epithelial cells by the CagA protein. In fact, high production of pro-inflammatory cytokines (L8, IL6, IL1 α, IL1 β) in the stomach has been found in patients infected with CagA(+) *H. pylori* strains.

The serine protease HtrA also plays a main role in the pathogenesis because enables the translocation of CagA and aids *H. pylori* to transmigrate across the epithelium [66,67].
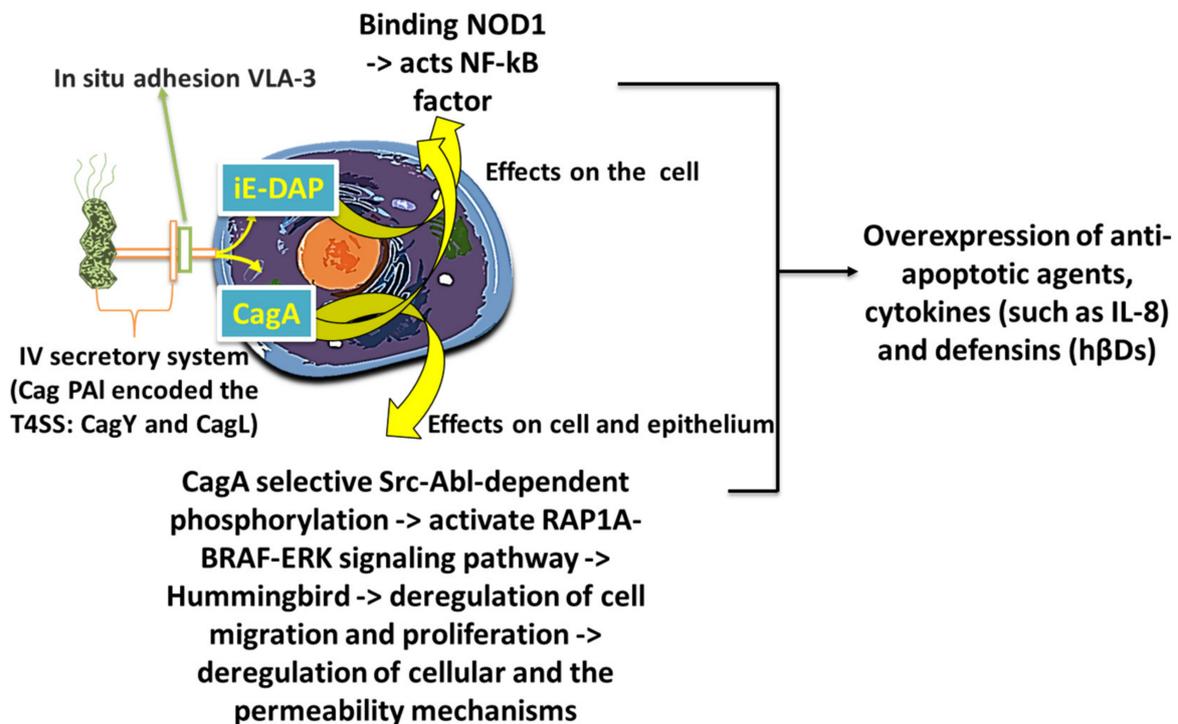
Figure 7. The cag pathogenicity island (cag-PAI) of the genome is composed of two main sections: cag I and cag II. Its genes encode the type IV secretory system (T4SS) necessary for the intracellular transport (from the bacterium to the host cell) of the CagA protein and peptidoglycan (iE-DAP). After the entry of CagA into the host cell, its Src-Abl-dependent phosphorylation occurs, which activates the RAP1A-BRAF-ERK (Ras-related protein 1-BRaf proto-oncogene serine/threonine kinase - Extracellular signal-regulated kinase) signaling pathway. This leads to the hummingbird phenotype (rearrangement of the actin-based cytoskeletal phenotype characterized by long, thin cellular extensions regulated by Rho GTPases and the Actin Related Protein (Arp) 2/3 complex) and the deregulation of cell migration and proliferation. Subsequently, due to the rupture of the apical junctions and the loss of membrane polarity, it leads to deregulation of cellular permeability mechanisms. Furthermore, CagA suppresses the apoptotic activity of VacA and activates the signaling pathway of the factor NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), allowing the subsequent overexpression of anti-apoptotic agents, interleukin (IL)-8, and defensins (hβDs). *H. pylori* causes apoptosis accompanied by increased expression of the pro-apoptotic multi-domain proteins Bax (Bcl-2-associated X protein) and Bak proteins that favor apoptosis, suggesting that Bax and Bak may be important mediators of gastric epithelial cells of apoptosis [68–71].

2.3. The Associated Diseases

Colonization of the stomach by *H. pylori* in most patients can cause acute gastritis or chronic non-atrophic gastritis (diffuse antral predominant gastritis or superficial gastritis) from the first moment of infection at the site of colonization (Table 3). Therefore, we can have acute gastritis and also a severe neutrophilic gastritis with transient hypochlorhydria. Infection causes no symptoms in about 80% of those infected. Histologically, an inflammatory infiltration of the stomach wall is observed in which *H. pylori* bacteria are found [71–73]. Inflammatory infiltration is limited in the pyloric area, while inflammatory lesions are limited or not observed in the stomach body. This is due to the production of ammonia which is cytotoxic (to counteract and regulate the pH in its favor) together with proteases, some phospholipases, vacuolating cytotoxin A (VacA), and the *CagA* gene (potentially carcinogenic). Additionally, cysteine-rich Hcp proteins (particularly HcpA), in turn, cause inflammation by triggering host immune responses. Finally, the bacterium

also increases cyclooxygenase-2 (COX-2) levels in chronic gastritis, which can probably be the basis for extragastric diseases [71,74–76]. *H. pylori* is the main agent of peptic ulcer, and not all patients can develop this condition (the reason still remains unknown). On the other hand, 20% of patients with *H. pylori* infection will develop peptic ulcer during their lifetime. Ulcers in the stomach and duodenum occur when the consequences of inflammation destroy the mechanisms that protect the mucous membranes from stomach acid and pepsin [73,74]—hence, the site of *H. pylori* colonization, and the one that will be affected by the two factors. *H. pylori* colonizes the pyloric antrum in subjects with large acid production, whereas in those producing normal or small amounts, it can colonize various locations in the stomach. If it is then located near the pyloric antrum, the inflammatory response induces the G cells of the antrum to secrete gastrin, which stimulates the parietal cells that increase the secretion of acid which damages the duodenum, causing ulcers with an increase in these cells over time [75]. When colonizing other sites in the stomach, the inflammatory response can cause gastric atrophy and, ultimately, ulcers, increasing the risk of cancer [73,76]. Finally, the growth hormone-releasing peptides (GHRPs) that inhibit normal food intake and reduce gastrointestinal motility, which increases after eradication therapy of *H. pylori*, decrease [77]. Thus, another disease associated with *H. pylori* is gastric cancer (>50% of adenocarcinomas), and it was suggested to be a high risk factor for stomach cancer in 1991; in 1994, the World Health Organization classified *H. pylori* as a type I carcinogen and the National Institutes of Health (NIH), USA, recommends eradication of the bacterium in peptic ulcer as a definite curing treatment. Later, in 2001, the first observational trial confirmed that *H. pylori* eradication prevents gastric cancer [24]. According to data in the literature, approximately 1–3% of infected patients in the world develop gastric cancer compared to 0.13% of people with no infection. Regarding stomach cancer, the WHO, in 2020, reported that incidence cases before the age of 75 are in fifth place for males (7.2%) and seventh for women (4.1%) [78,79]. It is certain that intestinal type cancer, and, to a lesser extent, cancer of the diffuse type, is more common in patients with *H. pylori*. Among the patients at risk, those with atrophic multifocal gastritis and concomitant intestinal metaplasia are those who have the highest risk of gastric carcinogenesis. Instead, the specific form of gastric cardias cancer is not associated with *H. pylori*. Over time, two probable theories about cancerogenesis have been developed. The first hypothesis takes into account the increased production of free radicals near the *H. pylori* infection site and an increase in the mutation rate of host cells from double-stranded DNA breaks [80]. Gastric inflammation is characterized by infiltration of neutrophils and macrophages into the epithelium, leading to an increase in pro-inflammatory cytokines, and they are reactive to oxygen (reactive oxygen species, ROS) and to nitrogen (reactive nitrogen species, RNS). This would cause damage to DNA, including the 8-oxo-2'-deoxyguanosine (8-OHdG) [81]. The presence of the cytotoxic gene cagA can increase 8-OHdG more in the gastric cells than in non-presence of this gene in certain *H. pylori* strains. The second hypothesis assumes that *H. pylori* induces inflammation and locally elevated levels of TNF-α and/or interleukin 6 (IL-6). According to the perigenetic mechanism, the increase in inflammation of Tumor necrosis factor alpha (TNF-α) and/or interleukin 6 (IL-6) leads to an alteration of the cells of the gastric epithelium. Therefore, it will lead to an alteration of their union, resulting in dispersion and migration without occurring in additional mutations of the tumor suppressor genes. This proposed mechanism has been called the perigenetic pathway [82–84]. Finally, the gastric stump can also be infected by *H. pylori* or Epstein–Barr virus (more frequent). It is considered a long-term precancerous condition that can progress to cancer. In fact, gastrectomy (distal or proximal) is a carcinogenic risk factor for several reasons. The etiopathogenesis could be related to duodenogastric reflux, hypergastrinemia, atrophic gastritis, and achlorhydria, and some polymorphisms of cyclooxygenase-2 (COX-2) and interleukin-1β (IL-1 beta) could also probably be involved. Furthermore, it has been noted that *H. pylori* eradication therapy may reduce the risk of carcinogenesis in patients undergoing previous gastrectomy for early gastric cancer. It has been noticed that bile reflux interferes with the prevalence of *H. pylori* infection because it also has bactericidal action

against this bacterium. However, this carcinogenic correlation with *H. pylori* appears to be rare. To improve the prognosis of gastric stump cancer, surveillance endoscopies of the gastric remnant and anastomosis site with multiple gastroenterostomy biopsies should be performed [85,86]. Finally, *H. pylori* is associated with a lymphoma derived from mucosa-associated lymphoid tissue (MALT) [87]. From the various research data, three main considerations emerge. The first is that after infection of the gastric mucosa, a percentage of patients develop a clonal hyperplasia of B lymphocytes, lymphatic tissue of the mucosa, and, therefore, a lymphatic tissue (which does not normally exist). The second is that this tissue (MALT) is probably malignant in some patients, giving rise to lymphoma in 72–98% of patients with MALT lymphoma that carry *H. pylori*. Finally, the third highlights that the eradication of the bacterium is not sufficient for the complete disappearance of low-grade MALT lymphoma. Other mucosa-associated lymphomas in *H. pylori* carriers may arise from lymphoid tissue in the esophagus, colon, rectum, and around the periorbital area of the eye (extranodal marginal zone B cell lymphoma). Therefore, it remains unknown why MALToma does not occur in all patients [24,86,88]. In a first study in 1997, other subsequent researchers noted the remission of the pathology for 62–95% of patients after the eradication of the bacterium as a cure in low-grade MALT lymphoma [89–92].

Table 3. The main *H. pylori*-associated diseases.

H. pylori Infection Associated Diseases	
Digestive Tract	**Extra-Digestive**
• Acute gastritis • Chronic atrophic gastritis • Gastro-esophageal reflux • Ulcers of the stomach, and duodenum • Esophageal cancer • Gastric adenocarcinoma (occurring in less than 20% of cases) • MALT lymphomas • Non-alcoholic steatohepatitis, hepatic fibrosis, liver cancer	• Cardiovascular (atherosclerosis and coronary artery disease) • Respiratory (chronic bronchitis, chronic obstructive pulmonary disease (COPD), bronchiectasis, lung cancer) • Skin (rosacea, chronic urticaria, chronic idiopathic urticaria, psoriasis, alopecia areata, nodular acne, atopic dermatitis, smooth lichen) • Hematological (plasma cell dyscrasias, pernicious anemia, iron deficiency anemia, idiopathic thrombocytopenic purpura) • Immunological (antiphospholipid syndrome, Henoch–Schönlein purpura, autoimmune neutropenia, autoimmune skin diseases, reactive arthritis, various allergies) • Neurological (multiple sclerosis, Parkinson's disease, Guillain–Barré syndrome, Alzheimer's disease) • Oral (periodontitis) • Ophtamological (central serous chorioretinitis, open angle glaucoma, blepharitis, spot blindness) • Diabetes mellitus, metabolic syndrome

Extra-digestive diseases associated with *H. pylori*, for the most part, derived from epidemiological studies via case–control studies. In 2000, in the Maastricht II Consensus Report, for the first time, a relationship between *H. pylori* and other extra-digestive diseases was revealed. Hence, a high antibody positivity for *H. pylori* was detected in patients with coronary heart disease, rosacea dandruff, and active bronchiectasis. The association between peptic ulcer and atherosclerotic ischemic lesions was already known based on necropsy or surgical patients' studies. It was considered that a diet rich in dairy products for the treatment of ulcers was sometimes considered to cause atherosclerotic lesions over time [24,93]. The prevailing pathogenetic opinion is that the chronic activation of

inflammatory mediators induced by *H. pylori* contributes to the occurrence of non-specific inflammatory reactions such as those observed in the diseases mentioned above [94].

In 1999, for the first time, it was noted that in coronary patients, there is an increase in the prevalence of CagA(+) *H. pylori* strains. Subsequent prospective studies involving many patients confirmed this result [24,95,96]. In most cases, the difference in CagA(+) *H. pylori* strains between patients and controls was statistically significant at the level of $p < 0.001$. Indeed, in some studies, a difference was only observed in CagA(+) and not in all *H. pylori* strains. In conclusion, a review of the literature leads to the conclusion that there is, to some extent, an association between *H. pylori* infection and ischemic myocardial disease, and therefore, various hypotheses are proposed (Figure 8) [97]. According to one theory, infection/inflammation in the stomach is due to the release of a number of pro-inflammatory cytokines, mainly interleukins (IL-8, IL-6, IL-1a, and IL-1b) and anti-TNF, that can increase the risk of coronary events [98]. In addition, it is noted that the intracellular activity of the CagA protein provokes an inflammatory response and higher concentrations of pro-inflammatory cytokines that are finally re-contracted in patients with CagA (+) infections in the stomach. The second hypothesis is that the lower B_{12} absorption in these patients results in a consequent increased homocysteinemia, which is a factor predisposing patients to coronary artery disease. Finally, the infection can lead to a procoagulant state which will lead to atherogenesis [99]. Among the proteins of *H. pylori* is hsp60, which is also a vascular endothelial antigen, and a cross-reactive autoimmunity reaction may develop. This can cause endothelial damage by producing autoantibodies that destroy the vascular endothelium. However, this concept is purely theoretical since, at least up until now, no such antibodies have been detected in patients. Patients with the bacterium have a reduced plasma HDL (High-Density Lipoproteins), which can also lead to atherosclerosis. Finally, a hypothesis would be that the increase in free radicals due to the decrease in antioxidants could induce an increased risk of coronary heart disease, but it has not been proven [100].

- Infectious hypothesis -> increase proinflammatory factors
- Decreased B12 absorption -> hyperhomocysteinemia
- Cross-reaction -> autoimmunity
- Hypercoagulability -> atherogenesis
- Reduction of plasma HDL -> atherogenesis
- Reduction of plasma antioxidants?
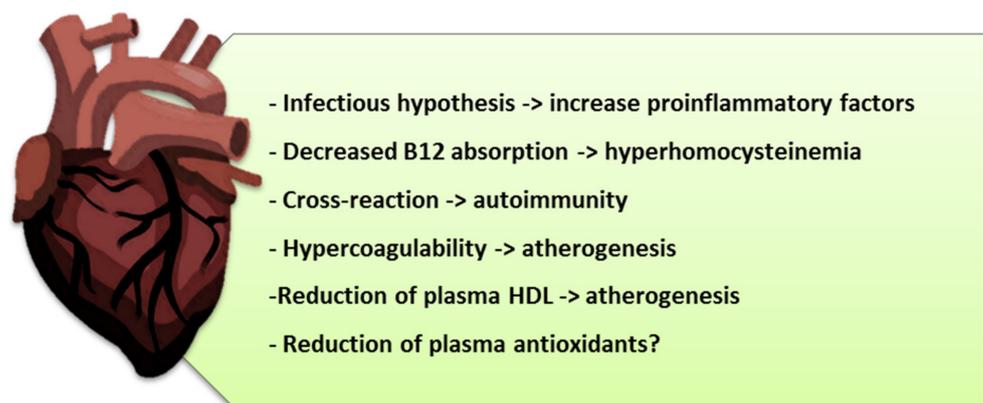
Figure 8. Pathogenetic hypothesized mechanisms on the correlation between *H. pylori* atherogenesis and coronary heart disease.

It has long been known that patients with peptic ulcer have a higher prevalence of chronic obstructive pulmonary disease (COPD) and active pulmonary tuberculosis than the general population. It is known that chronic inflammation and autoimmune activation reactions have been implicated in the pathogenesis of many respiratory diseases such as chronic bronchitis and bronchiectasis [101]. Hence, several studies have investigated a possible association between *H. pylori* infection and respiratory diseases such as chronic bronchitis, active pulmonary tuberculosis, bronchiectasis, and lung cancer. Chronic bronchitis was associated with peptic ulcer after a long time of identification of *H. pylori*. In 1998, in a prospective pilot study on a sample of 60 patients with chronic bronchitis, it was found that they had a higher prevalence of *H. pylori* infection than healthy subjects. Subsequently, a larger epidemiological study in 2000 showed that IgG (Immunoglobulin G) positive for

H. pylori had a particularly high prevalence of chronic bronchitis in women. It has been shown that pro-inflammatory cytokines (interleukins and tumor necrosis factor-α) are also involved in the pathogenesis of chronic bronchitis by promoting non-specific inflammation of the bronchial tree [102]. Thus, it can be assumed that *H. pylori* infection can cause bronchitis through the action of the produced cytokines and in combination with environmental, genetic, and other unknown factors. A possible translocation of *H. pylori* into the respiratory tree leading to chronic inflammation has been hypothesized (the bacterium was also cultured in the tracheobronchial secretions but was not found in histological preparations from bronchial tissue, nor was it isolated from bronchial alveolar lavage (BAL)) [103]. The reaction leading to bronchiectasis may be caused by the activation of systemic inflammatory mediators from chronic *H. pylori* infection. Pro-inflammatory cytokines (interleukins and tumor necrosis factor-α) are involved in the pathogenesis of COPD. Therefore, it can be deduced that *H. pylori* infection could, through pro-inflammatory action and in combination with the social environment and idiosyncrasy of the patient, have a role in the pathogenesis of COPD. Several studies have shown that chronic bronchitis is more common in anti-*H. pylori* IgG positive cases and has a higher prevalence of infection compared to healthy subjects. Hence, patients with peptic ulcer show a higher prevalence for COPD [101,102].

The association between *H. pylori* and skin diseases would be due to endogenous or exogenous vasodilatory factors and was noted many years before. Chronic idiopathic urticaria in many studies has an epidemiological link, but for others, there are opposite reports [103,104]. Rosacea is a relatively common inflammatory skin condition. Initially, a particularly high prevalence of *H. pylori* infection was reported in patients with rosacea. The disease remission observed after *H. pylori* eradication has not been assessed, as antibiotics given as an eradication treatment are, at the same time, effective drugs against rosacea. Other diseases have occasionally been associated with *H. pylori,* mostly supported by case reports or small studies such as alopecia areata, nodular acne, psoriasis, atopic dermatitis, and lichen planus [105].

The hypothesis that *H. pylori* infection may be a cause for some autoimmune diseases has been known for 20 years ago. Sjogren's syndrome was one of the first extra-gastric diseases to be associated with infection, and a recurrence associated with successful eradication therapy has been described. These studies involved small numbers of patients, possibly due to the rarity of the syndrome. Henoch–Schönlein purpura is a rare disease and there are two case reports in the literature in which complete reversal of the symptoms was found after eradication of the bacterium. Other implicated diseases have been considered, e.g., autoimmune thrombocytopenia, autoimmune thyroiditis, and acute autoimmune polyneuropathy. Hypotheses have been advanced that the high concentration of inflammation mediators or the antigens of the bacterium itself cause the production of autoantibodies through a cross-reactive mechanism that can be correlated with *H. pylori* infection [106].

In patients with chronic cholecystitis, primary biliary cirrhosis, and primary sclerosing cholangitis, genetic material of *H. pylori* was detected by PCR. Therefore, regarding hepatic cirrhosis and *H. pylori*, they are still controversial. However, it seems to link the infection to a complication of cirrhosis, which is encephalopathy. It appears that in most studies in cirrhotic patients with encephalopathy, they have a significantly higher rate of *H. pylori* infection than in cirrhotic patients without hepatic encephalopathy. However, references to the contrary are not absent from the literature. This relationship breaks down the justification that *H. pylori* has a high ammonia production due to the increased activity of urease and cannot be easily catabolized in the diseased liver [107–109]. However, research data from clinical trials on the role of *H. pylori* in biliary diseases are conflicting, as only a few strains of *H. pylori* can survive in the gallbladder (*H. hepaticus, H. bilis, H. rappini*, and *H. pullorum*). Therefore, although some of these strains have been isolated from histological preparations of patients with chronic cholecystitis, the clinical significance of this finding remains obscure. Other diseases associated with *H. pylori* are type I diabetes mellitus, chronic

pancreatitis, glaucoma, idiopathic thrombocytopenic purpura, iron deficiency anemia, and angioneurotic edema but also some neurological and ophthalmological ones [109,110].

2.4. Microbiota and H. pylori Interactions

The human microbiota is the set of microorganisms (approximately 10,000,000 different species), mostly bacteria but also archaea, fungi, and viruses, located in the various parts of the human body (such as oral, gut, and others). In particular, one of the most important parts is that of the intestinal microbiota because there is cross-talk with the gut/lung, gut/brain, and gut/skin which influences the host immune homeostasis. This ecosystem includes numerous microorganisms which belong to approximately 500 different genera [111]. The intestinal microbiota overcomes other functions such as aiding the digestion and absorption of food, the synthesis of vitamins, the catabolism of biomolecules, the metabolism of bile salts, and the regulation of inflammatory reactions. The disruption of this symbiotic balance (eubiosis) can create local and general homeostasis problems of the immune system as it would lead to dysbiosis, which, in turn, can lead to an increase in pathogens such as *Candida albicans* [112,113]. Common causes of disruption to the intestinal microbiota are alcohol abuse, reckless use of antibiotics, or infectious agents (such as *H. pylori*), which can lead to significant metabolic (such as obesity), inflammatory, and allergic disorders and even to precancerous conditions [114–123]. Therefore, if the population of one genus of microbes decreases or increases, it can affect populations of other genera by disrupting the overall balance of the intestinal microbiota and both innate and acquired immunity. An immune system acts in the gut mucosa (gut-associated lymphoid tissue, GALT), whose function is induced by the intestinal microbiota through antigenic stimuli, influencing both cellular and chemical stimulation of innate immunity (80% of B lymphocytes are detected in the gut) [123,124]. It has been noted that during *H. pylori* infection, there is an increase in the facultative pathogen *Haemophilus* spp., but there is also a decrease in the genera *Parasutterella* and *Pseudoflavonifractor* (important producers of SCFAs (Short-chain fatty acids) that modulate the immune response through regulatory T cells). In addition, an abundance in *Bacteroides* and *Prevotella* was noted. This condition can lead to an imbalance of the three cross-talking axes, causing global imbalance of the body's homeostasis [124–128].

2.5. The Diagnosis Over Time

The various methods of diagnosing *H. pylori* infection can be divided into non-invasive and invasive. The rapid urease test (*Campylobacter*-like organisms test, CLO-test) is based on the property of *H. pylori* to produce urease, as we have described. For the test, material from the stomach is taken and then immersed in a urea substrate. If there is a decomposition of the substrate and production of ammonia and carbon dioxide which varies the pH, such a variation (detected by an indicator, it can change color) is positive for the presence of *H. pylori* [129]. In addition, gastric biopsy samples can be used to determine the type of eventual gene mutations to demonstrate resistant clarithromycin strains in patients being treated or to be treated. Such a biomolecular assessment of resistance to clarithromycin and the search for *H. pylori* strains can be performed by fluorescent in situ hybridization (FISH). This resistance was found to be associated with point mutations in domain V of 23S rRNA in the 50S ribosomal subunit. This has a blocking effect on the link between the antibiotic and the ribosome, and consequently, protein synthesis is not inhibited by the drug. Furthermore, mutations have also been found in A2143G, A2144G, A2143C, and T2182C, which cause resistance to clarithromycin in *H. pylori* strains [130,131].

An accurate method is histological diagnosis after endoscopy and biopsy. To confirm the diagnosis, usually, four biopsies (two from the curves and two from the stomach body) are required. Subsequently, *H. pylori* in the histological specimen is detected by staining with hematoxylin–eosin. Biopsy culture has high sensitivity and is applied to determine the susceptibility of antimicrobial *H. pylori* strains [132]. In 1990, for the first time, the non-invasive 13C urea breath test (UBT) was introduced [24]. The breath test is a non-invasive testing procedure which is based on the property of *H. pylori* to produce urease, which is also used to test the successful eradication of the infection. The sensitivity of the method is low, as small concentrations of *H. pylori* are not detected. The subject is fed 13C-labeled urea, and the concentration of 13C in the exhaled dioxide is then measured [24,133]. Finally, PCR and detection of *H. pylori* antigen in stool, and fecal culture, are less used in clinical practice and mainly at the experimental level. In the mid-1980s, the first serological tests appeared to diagnose *H. pylori* infection. These became particularly useful due to the rapidity of the results and the low cost. Serological tests are divided into qualitative and quantitative. Whole blood is used in quality tests, and the results are available within minutes and are characterized by low sensitivity and, therefore, should not be used in either clinical practice or research protocols. Quantitative tests are based on the enzyme-linked immunosorbent assay (ELISA). This method detects the concentration of antibodies against *H. pylori* in blood serum, not whole blood, and the titer that is evaluated as indicative of the presence or absence of infection is that of IgG antibodies. In addition, the ELISA method offers the possibility of detecting CagA(+) [24,134].

The value of serological tests is important when considering the difficulty of finding *H. pylori* in biopsies from areas with atrophic gastritis. Recent studies have demonstrated the superiority of serological tests over biopsy examination for patients with atrophic gastritis. The main factor affecting their reliability is previous treatment for *H. pylori* eradication. However, relatively recently, laboratory methods for determining the concentration of IgG antibodies from other biological fluids (urine, saliva, smear, and mouth) have been developed. Recent studies have shown that these methods have particularly low sensitivity [24,134,135].

2.6. New Therapeutic Issues

The steps of treatment against helicobacter started long ago [24]. We must mention that in 1968, John Lykoudis (Ιωάννης Λυκούδης, 1910–1980, Greece) was the first to attempt a treatment regarding gastritis and peptic ulcer with three types of antibiotics (2 quinolines, 5,7-diiode-8-oxyquinolein 0.125 g; 5-iodo-7-chlorine-8–oxyquinoline 0.125 g, and strepto-mycin sulfate 0.075 g) together with vitamin A. He called this therapy "Elgaco", with a therapeutic scheme of 6–8 times a day for 10 days. He was convinced that the true cause was infectious. He treated himself and about 50,000 of his patients, but his observations "Ulcer of Stomach and Duodenum" in the *Journal of the American Medical Association* were, unfortunately, rejected. Finally, Lykoudis presented his therapy to the Greek National Medical Association but was rejected by the medical establishment [14]. However, after the time of treatment assessments, in 1987, the relapse of duodenal ulcer was shown to be reduced by bismuth, and in 1989, proton pump inhibitor (PPI)–amoxicillin dual therapy was proposed. However, in 1990, compliance and resistance were recognized as difficulties in treating infection. As we mentioned, the resistance to clarithromycin of certain *H. pylori* strains depends on point mutations in the 50S ribosomal subunit, so the antibiotic can no longer block bacterial protein synthesis. The first study in 1990 confirmed that the cure for duodenal ulcer will be healing from the *H. pylori* infection, and in 1992, trials for proposed vaccines started. In 1994, the first trials with PPI triple therapies for ulcer treatment began; in 1996, the Maastricht I Consensus Report (and later, the other report), screen-and-treat strategy was proposed over time, and in 2010, the bismuth quadruple therapies were revisited [23,24,130]. All patients with gastric or duodenal ulcers who are positive for *H. pylori* should receive primary treatment for the eradication of the bacterium, which is based on a proton pump inhibitor and is given in combination with two antibiotics for

7 days. The treatment has a 90% success rate, although there are factors that can influence its success, e.g., patient compliance, side effects, and microbial resistance to clarithromycin or metronidazole. In case of failure of the first treatment, second-line treatment should be performed, while in the case of failure again, a third attempt with a quadruple regimen or long-term maintenance treatment with acid suppression is recommended. *H. pylori* and NSAIDs (non-steroidal anti-inflammatory drugs) are independent risk factors for gastric ulcer. It is not known whether people requiring long-term NSAID treatment should receive eradication treatment to reduce the risk of developing ulcers [136–138]. An indicative regimen of current *H. pylori* eradication therapy consists mainly of triple therapy, based on the association of a proton pump inhibitor (PPI) and two antibiotics: amoxicillin 2000 mg/day and clarithromycin 1000 mg/day; metronidazole 1000 mg/day and clarithromycin 1000 mg/day, or levofloxacin 250–500 mg and amoxicillin 1 g (or metronidazole 500 mg or clarithromycin 500 mg) twice/day. However, for multidrug-resistant *H. pylori* strains, the use of rifabutin in triple therapy also seems to be effective. The triple therapy must be given for 10–14 days and only in world areas with low clarithromycin-resistant strains (<15%) or where local *H. pylori* eradication rates reach or exceed 85%. Thus, the modality of treatment, according to the first therapy effects, can sometimes be not only concomitant (drug administration occurs simultaneously) but also sequential (administration of drugs in two periods)—e.g., 5–7 days of PPI associated with amoxicillin and, subsequently, another 5–7 days of different antibiotics such as clarithromycin and metronidazole while maintaining the administration of the PPI. In other cases, the initial therapy should be fourfold with PPI (lansoprazole 30 mg twice/day, omeprazole 20 mg twice/day, pantoprazole 40 mg twice/day, rabeprazole 20 mg twice/day, or esomeprazole 40 mg once/day), bismuth sub-citrate (524 mg four times/day), and two antibiotics (tetracycline 500 mg four times/day and 250 mg metronidazole four times/day). People who do not have a history of peptic ulcer or indigestion and are young do not need treatment, unlike older patients with a major comorbidity or a history of old peptic ulcer. Quadruple therapy is the best initial therapy in world areas where the clarithromycin resistance rate is > 15% and the treatment must be given for 14 days. The treatment is repeated if the *H. pylori* is not eradicated. If two cycles are ineffective, some specialists recommend performing an endoscopic examination to obtain cultures for susceptibility testing. Eradication of *H. pylori* can be confirmed at or after four weeks from the end of therapy by urea breath test or fecal antigen test, or by upper digestive tract endoscopy [137–139].

Finally, probiotics have been shown to act in a beneficial way against various diseases, including infectious ones, e.g., from bacterial, viral (such as in the current viral pandemic due to SARS-CoV-2), fungal, and other causes [139–147]. The ability of probiotics to be a valid adjuvant in the eradication therapy for *H. pylori* infection (therefore, against growth) is in its role in bringing the gut into eubiosis, including secretion of antimicrobial substances, competition at the adhesion site of epithelial cells, and stabilization of the mucosal barrier [26–29], and there may be some hypotheses regarding the beneficial effects of probiotics. Several studies have confirmed that probiotic supplementation is able to facilitate eradication and reduce the incidence of side effects of antibiotic therapy. In particular, the use of probiotics with various selected species is more advantageous than monospecies preparations (such as *Lactobacillus* spp. or *Bifidobacterium* spp.). The combination of strains *L. reuteri* DSM 17938 and *L. reuteri* ATCC PTA 6475, or supplementation with *S. boulardii*, has demonstrated positive effects [148,149].

3. Discussion

As we mentioned, successful colonization of the gastric epithelium by *H. pylori* depends on the action of bacterial-dependent mechanisms such as pH control through urease, inactivation of oxygen and nitrogen free radicals produced by neutrophils, and activation of bacterial DNA repair/recombination signaling pathways along with the ability to integrate extracellular DNA into the bacterial chromosome that promotes genetic differentiation. Furthermore, the production of various inflammatory mediators such as IL-1, IL-8, and

TNF-α due to the recognition of bacterial derivatives (VacA, LPS, neutrophil activation factor (NapA), porine) and the elimination of recognition of *H. pylori* by Toll-like receptor (TLR) sensors, and the consequent modulation of anti-inflammatory agents, establish chronic infection [150]. Furthermore, immune responses of types Th1 and Th17 are observed, regulated by the cytokines IL-23 and IL-12. The inability of the mechanisms of natural immunity to recognize and eliminate *H. pylori* leads to the development of acute inflammation and to the attraction of macrophages and T and B lymphocytes and selective differentiation with concomitant Treg (Regulatory T cell) differentiation [151]. This condition further allows the bacterium to escape from the host's immune processes. Indeed, numerous studies indicate that the possible presence of polymorphisms in the genes of inflammatory cytokine cells IL-1β, TNF-α, and of the anti-inflammatory cytokine IL-10 determines the intensity of the inflammatory response. All this constitutes a background that probably predisposes one to the oncogenesis induced by *H. pylori* [152]. Antimicrobial peptides (AMPs) are key components of natural gastric tissue immunity. The two main categories of AMPs are the two Ds (α- and β-defensins) and cathelicidin LL-37/hCAP-18. The secretion of human β-defensins (hβDs 1, 2, 3, and 4) in the gastric epithelium adapts it according to the presence of pathogenic microorganisms. *H. pylori* can colonize the gastric mucosa, escaping or possibly suppressing the mechanisms of natural immunity including AMPs. Furthermore, the ability to produce bio-membranes is of particular importance for a more complete understanding of the survival mechanisms of *H. pylori* in adverse gastric conditions and the pathogenesis of chronic infection. Finally, the role of HspA and -B, which are highly antigenic, in the pathogenesis of infection has not been noticeably clear [153–156]. The interactions of *H. pylori* Hsp-60 and TLR in host cells contribute to the development of gastric inflammation by the bacterium. Furthermore, reactions induced by immune cross-responses between *H. pylori* HspB and human Hsp-60 of the gastric epithelium may be involved in the development of MALT lymphoma [157,158]. In this regard, recent studies also show that CagA and HspB increase gastric cancer risk. Instead, Hsp-60, by inducing the secretion of inflammatory cytokines and promoting angiogenesis, triggers the onset of oncogenesis and, therefore, acts as a carcinogen [159]. Chemokines have chemotactic activity in leukocytes and are, thus, directly or indirectly involved in inflammatory reactions. They are classified into two main families (according to the position of the cysteine residues): C-X-C and C-C. The first has chemotactic properties in neutrophils (no monocytes) and the second has chemotactic properties in monocytes and lymphocytes with little effect on neutrophils. Infection then increases the production of C-X-C chemokines such as IL-8 and GROα (Growth-regulated oncogene α) and is associated with an inflammatory reaction without increased production of C-C chemokines. Furthermore, B cell-attracting (BCA)-1 induces chronic gastritis and is involved in the formation of MALT and gastric lymphomas in *H. pylori* infections [160–163]. Hence, BCA-1 assessment is a useful indicator of the development of MALT aggregates. Finally, the IL-8-251 T/A genotype is associated with an increased risk of peptic ulcer and duodenal ulcers in *H. pylori* infections. Instead, the IL-8-251 AA genotype represents an important indicator of the presence of gastric cancer. Furthermore, the bacterium reduces the production of the peptides trefoil factor (TFF)-1 and trefoil factor (TFF)-2, which play a role in the repair of the gastric mucosa (such as gastritis and ulcers) and suppress the processes of carcinogenesis (Figure 9) [164–170].

Finally, there are two main pathogenetic mechanisms that report pathogenic correlations between *H. pylori* and extra-digestive diseases. The first is the induction of the release of several pro-inflammatory agents such as cytokines, eicosanoids, and acute phase proteins by *H. pylori*. The second concerns the possibility of microbial antigens mimicking those of the host, resulting in activation of autoimmunity [91].
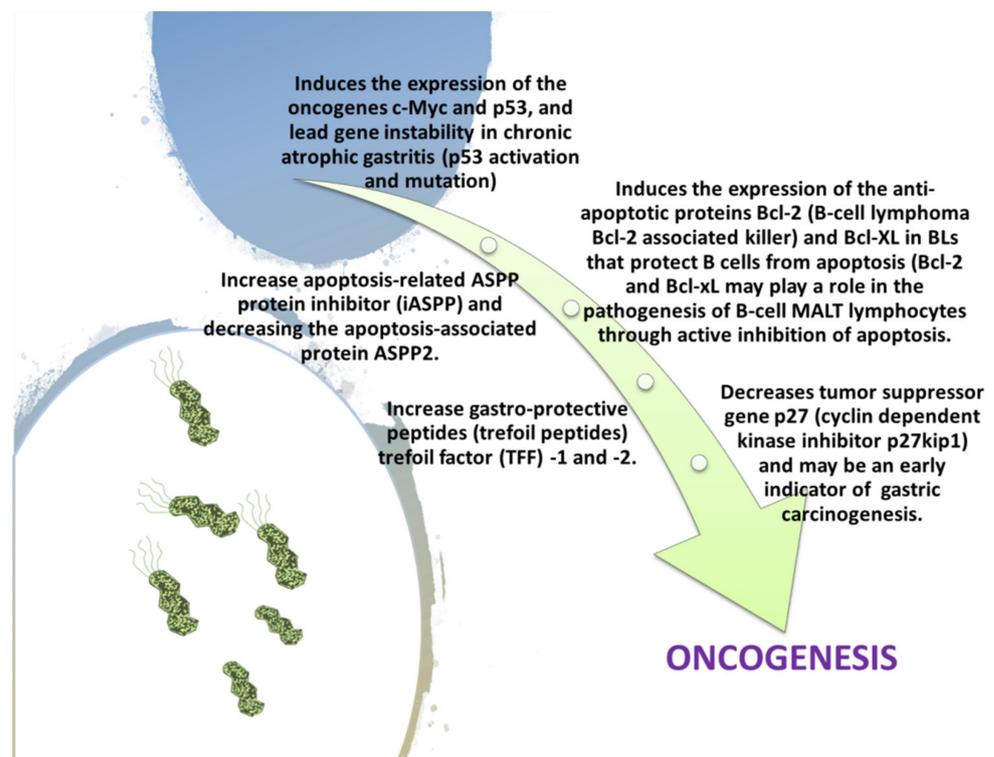
Figure 9. Other hypotheses about gastric oncogenesis pathways of *H. pylori.*

4. Conclusions

H. pylori was recognized as a pathogenic infectious agent for humans only in 1985. The recognition of the pathogenic role of *H. pylori* has revolutionized medicine and gastric and duodenal pathology. This has led not only to the new description of the etiopathogenesis of some diseases of the digestive system, but also to re-thinking the prevention and therapy. Epidemiological studies conducted in recent years have revealed that *H. pylori* infection represents an endemic disease all over the world. It is well established that *H. pylori* infection is acquired, in most cases, in childhood. We still must discover the relationships of individual and environmental factors by incidence and pathogenesis and correlations with other systems. Infection appears to be a representative indicator of socio-economic level, and at present, there is a significant reduction in the incidence of the disease worldwide and a steady decrease in the incidence of infection in childhood, probably due to better conditions of hygiene and improvement in treatment. Treatment must address compliance and antibiotic resistance during the disease. A compromising observation is the use of probiotics as adjuvants in the therapy because the microbiota can be altered by immune-mediated reactions of the organism against the bacterium.

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