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Helicobacter, Inflammation, and Gastric Cancer

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Abstract

Helicobacter pylori infection leads to long-lasting chronic inflammation and represents the most common risk factor underlying gastric cancer. Recently, new insights into the mechanisms through which *H. pylori* and mucosal inflammation lead to cancer development have emerged. *H. pylori* virulence factors, in particular specific *CagA* genotypes, represent main factors in gastric cancer, inducing altered intracellular signaling in epithelial cells. The chronic nature of *H. pylori* infection appears to relate to the VacA virulence factor and Th17/Treg mechanisms. A role of *H. pylori* infection in epigenetic and microRNA deregulation has been shown. Mutation of the epithelial cell genome, a hallmark of cancer, was demonstrated to accumulate in *H. pylori* infected stomach partly due to inadequate DNA repair. Gastric stem cells were shown to be targets of oxidative injury in the Helicobacter-inflammatory milieu. Recent advances emphasizing the contribution of bacterial factors, inflammatory mediators, and the host epithelial response in gastric carcinogenesis are reviewed.

Keywords

Helicobacter; *H. pylori*; Inflammation; Mutation; DNA repair; Gastric cancer; Stem cells; Pathobiology

Introduction

Gastric cancer (GC) is the most frequent malignancy arising in the stomach and represents the fourth most frequent cancer worldwide[1]. *Helicobacter pylori (H. pylori)* bacteria were identified as the main agent of chronic gastritis and ulcers by Warren and Marshal[2], and later studies revealed an association with GC[3], leading to the classification of *H. pylori* as a human carcinogen[4]. The attributable risk of gastric cancer related to *H. pylori* infection in the population has been estimated to be 75%[3].

Gastric cancers can be divided into distinct subtypes based on differential mechanisms of neoplastic initiation and underlying risk factors (inherited vs. sporadic), histopathologic, and molecular phenotypes. Sporadic type adenocarcinomas represent approximately 80% of all cases of GC and are associated with multifactorial causal factors, among which *H. pylori* chronic gastritis represents a main driving factor. Additionally, other factors known to play a role in GC development include host genetic susceptibility and carcinogens present in specific diets or smoking that work together with other factors such as the cellular injury caused by chronic gastritis to enhance the risk of gastric cancer[5, 6]. The molecular subtypes of gastric cancer include tumors characterized by the chromosomal instability pathway (CIN), the most frequent molecular type of GC, while a smaller proportion of tumors

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develop through the microsatellite instability pathway (MSI), or the CpG island methylator phenotype pathway[7].

Gastric cancers are among the class of cancers that arise in association with chronic inflammation (chronic gastritis), as do other cancers in the gastrointestinal tract such as esophageal adenocarcinoma arising in association with reflux esophagitis and Barrett's esophagus, and colon cancers that arise in patients with inflammatory bowel diseases (ulcerative colitis and Crohn's disease). Although inflammation is a common factor in all these cancers, unique mechanisms that relate to specific factors involved in each type of cancer likely provide cancer signatures that may reflect the different underlying factors. To this end, in *H. pylori* associated GC, although inflammation is a major driver of neoplastic development, additional Helicobacter-specific induced alterations contribute to the landscape of molecular changes that may be unique to the *H. pylori*-cancer association. This notion is supported by studies showing that *H. pylori* bacteria affect epithelial cell regulation in the absence of inflammatory products as demonstrated in many co-culture studies, and the bacterium virulence factors, in particular the CagA protein, have been shown to induce a unique and complex array of cellular signaling alterations[8] (Figure 1).

Role of *H. pylori* in Gastric Carcinogenesis: Patterns of Host Response

The chronic nature of *H. pylori* gastritis is critical to the carcinogenic potential of this infection, resulting in a long-term interaction of the bacteria and inflammatory mediators with gastric epithelial and epithelium progenitor and stem cells, with accumulation of mutations, epigenetic modifications and deregulation of cell function that may ultimately lead to neoplasia. Therefore, *H. pylori* infection plays a critical role during the initiating steps of gastric cancer. *H. pylori* infection is usually acquired during childhood, with ensuing chronic gastritis as the norm and various possible complications including gastric and duodenal ulcers, gastric cancer, and extranodal marginal zone B-cell lymphoma of mucosa associated lymphoid tissue (MALT-Lymphoma)[9, 10]. Cure of *H. pylori* infection requires treatment with anti-*H. pylori* therapy[11]. Gastric cancer develops several decades after acquisition of the infection, following progressive mucosal damage secondary to continued interaction of *H. pylori* bacteria with the mucosa and the consequent chronic inflammatory milieu[12].

Histologically, *H. pylori* gastritis is characterized by a combination of chronic and acute inflammation of the gastric mucosa. There is progressive damage of gastric glands that leads to mucosal atrophy with intestinal metaplasia, overall resulting in a picture of atrophic gastritis, which constitutes an environment with enhanced risk of development of dysplasia and carcinoma. Extensive gastritis and mucosal atrophy in the gastric body and fundus lead to hypochlorhydria, which creates an environment that allows for overgrowth of other bacteria that may increase carcinogenic activity in the stomach through the conversion of nitrites to carcinogenic nitroso-N compounds[13]. *H. pylori*-associated pangastritis (involving both the body/fundus and antrum) is frequently seen in family relatives of gastric cancer patients, which may contribute to gastric cancer clustering in some families[14]. The histologic alterations that precede gastric cancer, including intestinal metaplasia, represent pre-neoplastic epithelial changes in gastric carcinogenesis and have been shown to carry numerous genomic, epigenetic and functional abnormalities that can also be detected in cancer tissues[6, 15–18]. Therefore, characterization of molecular alterations in the background mucosa before patients develop GC may offer an opportunity to identify patterns associated with increased risk of GC development.

The cancers arising in the inflammatory background of *H. pylori*-associated chronic gastritis are most commonly of intestinal type, which are predominantly well-to moderately-

differentiated adenocarcinomas, but diffuse type adenocarcinomas, which are poorly cohesive and poorly differentiated and may include a variable component with signet ring cell features, also occur in association with *H. pylori*[19, 20].

H. pylori Infection and Inflammatory Host Response

H. pylori infection of the stomach elicits both humoral and cellular immune responses[21]. The induced immunologic/inflammatory cascade reflects the activation of innate and acquired immune responses[21]. The characteristic long-term chronic inflammatory status of *H. pylori* infected gastric mucosa requires evasion of *H. pylori* from the immune system. The immune response to *H. pylori* is induced by bacterial products upon their contact with epithelial cells of gastric mucosa, and with macrophages and dendritic cells in the lamina propria that are reached after epithelial cells and intercellular junctions are damaged by *H. pylori* virulence factors such as the VacA toxin. Epithelial cells respond to *H. pylori* by undergoing cellular signaling changes and by releasing cytokines into the mucosal lamina propria, to activate macrophages, dendritic cells and other inflammatory cells. Inflammatory mediators released during *H. pylori* gastritis include interleukin IL-1, IL-6, IL-8, tumor necrosis factor (TNF)-alpha and regulated and normal T cell expressed and secreted (RANTES)[22]. Mediators released by macrophages, dendritic cells and epithelial cells activate T-lymphocytes with a predominant Th1 response[23], regulatory T-lymphocytes (Treg), B-lymphocytes which mature into mucosal plasma cells, and neutrophils which actively phagocytize *H. pylori* bacteria. In addition, there is a contribution of dentritic cells that release IL23 and activate the production of IL17 associated with a Th17 response against *H. pylori* [24]. However, studies indicate that *H. pylori* direct a Treg-skewed dendritic cell-induced helper T-cell differentiation, in contrast to the Th17-skewed response seen with pro-inflammatory bacteria. The increased Treg induction in *H. pylori* infected–hosts forces an imbalance of the Th17/Treg axis, which may lead to suppressed Th17 and ineffective bacterial eradication and persistence of *H. pylori* as a chronic infection[25].

H. pylori stimulates the production of growth factors such as granulocyte-macrophage colony stimulating factors (GM-CSF) and inflammation regulators such as cyclo-oxygenase-2 (COX-2) and reactive oxygen/nitrogen species (ROS/RNS).

NF-kB is a key regulator of inflammation and other cellular cascades that underlie carcinogenesis. NF-kB can be activated by numerous pro-inflammatory activators namely cytokines released by other cells and through Toll like receptor (TLR) activation by pathogen products, through two different pathways (the canonical and non-canonical pathways). *H. pylori* activation of NF-Kb follows either the canonical or non-canonical pathways in epithelial cells and lymphoid cells, respectively[26]. *H. pylori* peptidoglycan is recognized by epithelial cells through the intracellular nucleotide binding and oligomerization domain 1 (NOD1), activating MAPKs in both the NF-kB and AP1 pathways, leading to cytokine release[27].

Inflammatory mediators that have been implicated in inflammation related cancer development include IL1-beta, tumor necrosis factor (TNF-alpha) and IL-6. Il1-beta and TNF-alpha induce activation of NF-kB in epithelial cells, leading to cell growth/ proliferation, suppression of apoptosis, and release of other growth factors and cytokines such as EGF, IL-6, CO2 and ROS[28]. COX2 also enhances cell growth and angiogenesis, ROS modify protein function, IL6 activates STAT3 further enhancing cell growth and stimulating growth factor production including the Reg protein[28,29,30]. TNF-alpha and IL6 appear to create a positive feedback loop during cancer development, and also activate ERK/ MAPK cascades known to regulate cell proliferation, migration and angiogenesis[31]. In

addition, IL1-beta, TNF-alpha and IL-6 activate c-Jun kinase (JNK) resulting in cell death induced compensatory proliferation[28, 32,33].

Role of Stem Cells in *H. pylori* Associated Gastric Cancer Development

Gastric stem cells provide the capacity for renewal of all cell lineages of gastric epithelium. The molecular markers that identify epithelial stem cells in the oxyntic mucosa of gastric body and in the antrum appear to be different, consistent with the different cellular lineages that constitute gastric glands in these two different areas of the stomach[34]. Lgr5 was shown to mark epithelial stem cells in mice and human gastric antrum[35,36, 37]. In the oxyntic mucosa, trefoil factor family 2 (TFF2) was reported in progenitors for mucous neck, parietal and zymogen producing cells[38]. Another marker of progenitor cells in oxyntic mucosa may be doublecortin-like kinase (Dclk1)[39]. Other putative gastric stem cell markers are ADAM17, CD44, and Musashi-1[36, 40]. Bone marrow derived stem cells may contribute to the gastric stem cell pool in chronic gastritis and *H. pylori* associated neoplastic progression[41]. It has been postulated that the engrafted bone marrow derived stem cells may not follow a normal differentiation pathway and could undergo uncontrolled replication, progressive loss of differentiation, and neoplastic behavior[41, 42]. In recent studies, we reported that the Lgr5-positive epithelial stem cell pool is expanded in *H. pylori*-associated gastritis in the antrum of patients with GC. In GC patients with active *H. pylori* infection, Lgr5-positive epithelial stem cells may be more susceptible to DNA damage than Lgr5-negative epithelial cells, demonstrated by increased levels of nuclear 8-hydroxydeoxyguanosine (8-OHdG), suggesting that *H. pylori* infection may contribute to GC risk by affecting epithelial stem cells in the human stomach[37].

The potential interactions of inflammatory products or *H. pylori* released factors or direct bacterial interactions with stem and progenitor cells remain unknown and warrant further studies.

H. pylori and Virulence Factors in Gastric Carcinogenesis

A number of *H. pylori* virulence factors play a role in determining the patterns of disease associated with infection[8]. These virulence factors include the vacuolating cytotoxin (VacA), cytotoxin-associated antigen A (CagA) proteins, HP-NAP, oipA, and dupA[8]. The VacA toxin affects T and B-lymphocytes and contributes to the ability of *H. pylori* to establish persistent chronic gastritis[43]. VacA induces ROS production and mitochondrial DNA mutation in gastric epithelial cells, while HP-NAP induces release of ROS from neutrophils[33, 44].

The CagA protein is encoded by the *cagA* gene, one of the genes that constitute the Cag pathogenicity island, which encodes a type IV secretion system[8]. *H. pylori* strains carrying a *cagA* gene with specific structural variants have been shown to have a stronger association with GC[8]. The CagA type C strains were associated with more severe degrees of atrophic gastritis and gastric cancer[45]. *H. pylori* strains with phosphorylation at the EPYIA site of CagA proteins are more common in East-Asia than in Western countries, which may contribute to the increased incidence of gastric cancer in this region of the world[46]. There are several mechanisms by which CagA affects epithelial cells and may contribute to gastric cancer development[46]. CagA protein is injected from the bacterium into gastric epithelial cells via the type IV secretion system and then interacts with several intracellular signaling molecules in both tyrosine phosphorylation dependent and independent manners[46]. Once inside the epithelial cell CagA undergoes tyrosine phosphorylation by the epithelial cell Src protein and other signaling molecules at the EPIYA sites and binds Src homology 2 domain containing tyrosine phosphatase (SHP2), deregulating the phosphatase activity[46]. CagA-positive *H. pylori* induce higher levels of IL-8 and activate NF-kB, AP-1 and NFAT[47].

CagA was shown to interact with the hepatocyte growth factor receptor Met causing sustained activation of PI3K and Akt which leads to b-catenin and NF-kB activation[48]. CagA was found to interact with TNF receptor associated factor 6 (TRF6) and TGF-beta-activating kinase 1 (TAK1) with resulting NF-kB activation[33].

CagA related intracellular signaling potentially affects multiple cellular functions. For example, in our studies we showed that methylation of the O (6)-methylguanine-DNA methyltransferase (MGMT) DNA repair gene was significantly associated with CagA-positive *H. pylori* strains in chronic gastritis, suggesting a role for CagA-positive *H. pylori* mediated effects in epigenetic regulation[49]. Other effects of CagA involve interference with proteasome-mediated degradation of the tumor suppressor RUNX3 and TP53 by binding ASPP2, a modulator of P53 and gene silencing of RUNX3[50,51].

Studies in mice carrying a transgenic *cagA* gene showed gastric epithelial hyperplasia and some mice developed gastric polyps and adenocarcinomas of the stomach and small intestine[52], further supporting a role for CagA in gastric carcinogenesis.

Host genetic Susceptibility and H. pylori Associated Gastric Cancer

Although it is clear that development of GC is multifactorial and requires interaction with host susceptibility genetic factors, to date, only few host susceptibility factors have been confirmed, including the pro-inflammatory gene polymorphisms in *IL-1beta* and *IL-1RN* (receptor antagonist) genes which showed to increase the risk of hypochlorhydria, gastric atrophy, gastric cancer and neoplastic precursors in *H. pylori* infected patients[53].

Molecular Alterations Driving *H. pylori* Associated Gastric Carcinogenesis

From the early stages of *H. pylori* gastritis, the infection and associated inflammation lead to epithelial cell mutations, epigenetic, microRNA and gene expression changes, genomic instability, altered cellular signaling, and imbalanced proliferation and apoptosis of gastric epithelial cells[54], driving the progression from pre-neoplastic to neoplastic lesions[6] (Figure 1).

Oncogene activation and loss of tumor suppressor gene function are well known mechanisms involved in development and maintenance of the cancer phenotype, and are in many instances caused by mutation or by epigenetic regulation, whether directly through hypermethylation of gene promoter regions or indirectly through epigenetic control of transcriptional or post-transcriptional regulators such as miRNAs. To establish a parallel, in cancers arising in inflammatory milieus, such as gastric cancer, mutagenesis and epigenetic deregulation are main mechanisms driving epithelial cells in the direction of cancer. Increased mutation burden of the epithelial genome results through two established mechanisms: 1) increased occurrence of mutations due to direct damage of DNA (free radicals, primarily ROS and NOS), that can be enhanced by aberrant expression of mutation inducing factor (AID) and 2) deficient repair of mutations prior to DNA replication (deficient DNA repair associated with reduced function of MGMT[49] and mismatch repair (MMR) genes MLH1, MSH2 and MMR heterodimer associated proteins[55] (Figure 1). Published data support that both mechanisms are critical for *H. pylori* and inflammation associated gastric cancer[33, 49, 55]. The link between enhanced mutation burden of gastric epithelium and *Helicobacter* gastritis can be found at multiple levels as reviewed below.

Mutations in Gastric Carcinogenesis

The types of mutations and mechanisms of mutagenesis in gastric carcinogenesis are multiple and include microsatellite instability (MSI) resulting from altered DNA mismatch

repair, point mutations and genomic instability including loss of heterozygosity (LOH), gene amplifications, rearrangements, insertion and deletion mutations, chromosomal losses and duplications. These genomic lesions accumulate during the steps of gastric carcinogenesis in cells representing intestinal metaplasia, dysplasia/adenoma, and adenocarcinoma and probably in epithelial progenitors and stem cells[56].

Through the combined effects of *H. pylori* virulence factors and inflammatory mediators released in response to infection, ROS levels increase in the cell and lead to modification of nucleic acid bases leading to DNA damage including single of double-stranded DNA breaks, DNA adducts and DNA protein cross links[28].

Mutations of *TP53* and *APC* genes can be detected in intestinal metaplasia and gastric dysplasia[57, 58]. *TP53* mutations (in exons 5 to 8) characterized by G:C to A:T transitions are detected in gastric neoplasia[58]. *APC* mutations, including stop-codon and frameshift mutations were reported in 45% of cancers[59]. *KRAS* mutations in codon 12 are rare in gastric carcinogenesis and were reported in 14% of cases with atrophic gastritis, and about 10% of adenomas, dysplasias, and carcinomas[60]. Recently, the spectrum of mutations in gastric cancer has been explored by massive parallel sequencing approaches. A recent study performed whole exome sequencing in gastric cancer as compared to matching non-neoplastic tissue and determined the molecular pathways most frequently revealing gene mutations[61]. Chromatin modification and cell junction pathways showed the most significant enrichment of mutated genes. Mutations were found in members of the SWI-SNF complex (*ARID1A, PBRM1* and *SMARCC1*), ISWI complex (*SMARCA1*) and NuRD complex (*CHD3, CGD4* and *MBD2*), and other genes encoding histone-modifying proteins (*SIRT1* and *SETD2*), affecting 59% of gastric cancers[61]. Overall, 59% of gastric cancers had mutations in genes involved in cell adhesion, including *CHD1*. Genes involved in cell cycle regulation including *TP53, PTEN* and *TTK* were mutated in 77% of gastric cancers. Other signaling pathways frequently mutated in gastric cancers included the Wnt-BMP-TGF-beta, axon guidance, MAPK, DNA replication, focal adhesion, ERBB, ATR-BRCA and Rb pathways[61]. Another study also using exome sequencing reported that cell adhesion was the pathway most enriched for mutations[62]. *TP53* was mutated in 66.7%, and *PIK3CA* and *ARIDI1A* were mutated in 20% of gastric cancers[62]. Frequent mutations in chromatin remodeling genes (*ARIDI1A, MLL3* and *MLL*) were found in 47% of gastric cancers[62]. *ARIDI1A* mutations where associated with *PIK3CA* mutations and microsatellite instability[62]. Importantly, some mutations identified in the advanced cancer stages, may have occurred early during initiation associated with *H. pylori* infection (such as MSI[15]) whereas other mutations occur late in cancer progression and are independent of *H. pylori* infection or inflammation induced by the bacterium.

As summarized in Figure 1, the mechanisms through which *H. pylori*-associated gastritis results in enhanced mutagenesis and cellular deregulation are multiple. The increased DNA damage of epithelial cells is due to oxidative stress caused by reactive oxygen species (ROS), and reactive nitrogen species (RNS) generated by inflammatory cells as well as by gastric epithelial cells after activation by *H. pylori*[63]. In addition to the increased production of ROS, there is limited availability of oxygen radical scavengers, such as glutathione and gluthatione-S-transferase during *H. pylori* gastritis, which may contribute to higher levels of oxygen radicals in the mucosa of infected patients[64]. Gastric mucosa with *H. pylori* gastritis, intestinal metaplasia and gastric atrophy as pre-neoplastic lesions, was shown to have increased levels of DNA 8OHdG, a marker for oxidative DNA damage[65]. Mutations associated with oxidative damage include point mutations in genes such as the tumor suppressor *TP53, KRAS*, and other genes involved in gastric carcinogenesis[58]. Epithelial expression of the activation-induced cytidine deaminase (AID) in *H. pylori* gastritis may induce C/G to T/A transitions by its cytidine deaminase activity[28].

Specific deficiencies of DNA repair functions during *H. pylori* gastritis also contribute to *H. pylori* associated mutagenesis[6, 49, 66, 67]. Altered DNA repair mechanisms include those involved in DNA MMR as well as other proteins that primarily repair DNA lesions induced by oxidative and nitrosative stress, such as MGMT and polymorphic glycosylase (OGG1). DNA MMR proteins (MLH1, MSH2, MSH6 and PMS2) are required for the repair of DNA replication associated sequence errors. Several studies have reported a role for DNA MMR deficiency in mutation accumulation during *H. pylori* infection[15, 37, 49, 55, 66]. DNA mismatch repair deficiency leads to frameshift mutagenesis that can alter the coding region of genes, as well as repetitive regions known as short tandem repeats or microsatellite regions, with resulting microsatellite instability[68]. Microsatellite instability can be detected in chronic gastritis and intestinal metaplasia from patients with gastric cancer, indicating that MSI can occur in pre-neoplastic mucosa[15, 56]. For example, a study of microsatellite instability in the stepwise gastritis cancer sequence reported MSI in chronic gastritis (13% of cases), intestinal metaplasia (20% of cases), dysplasias (25% of cases) and gastric cancers (38% of cases), consistent with a role for DNA MMR deficiency in *H. pylori* associated gastric carcinogenesis[69]. Using a co-culture *in vitro* system, gastric cell lines exposed to *H. pylori* expressed reduced levels of DNA mismatch repair proteins MLH1 and MSH2[55], and these changes were associated with increased mutagenesis of a reporter vector, including MSI-type frameshift mutations as well as point mutations[66]. These studies provided definitive evidence that *H. pylori* bacteria lead to mutations in the epithelial cell genome, a hallmark of cancer.

High-level of MSI (MSI-H) is associated with loss of expression and promoter hypermethylation of the MLH1 DNA mismatch repair gene in gastric adenomas and cancers. MSI has been reported in 17–35% of gastric adenomas[70, 71], and in 17 to 59% gastric carcinomas[15, 70–74]. Gastric cancers with MSI-H may carry frameshift mutations that may affect the function of cancer related genes, such as *BAX, IGFRII, TGF RII, MSH3* and *MSH6*[75–79].

Other DNA repair proteins are involved in the correction of oxidative stress associated mutations during *H. pylori* infection such as repair of 8-OHdG by polymorphic glycosylase (OGG1). A gene polymorphism that may affect the function of OGG1 was reported frequently in patients with intestinal metaplasia and gastric cancer, suggesting that deficient OGG1 function may contribute to increased mutagenesis during gastric carcinogenesis[80]. The DNA repair protein MGMT can remove O (6)alkylG DNA adducts. In the absence of functional MGMT these adducts are not removed and mispair with T during DNA replication, resulting in G-to-A mutations. *MGMT*-promoter methylation has been reported in various stages of gastric carcinogenesis, suggesting a role for this DNA repair protein in gastric cancer development[81]. Hypermethylation of the *MGMT* gene and reduced levels of MGMT proteins in the gastric epithelium, particularly in patients infected with CagA-positive strains occur during *H. pylori* gastritis[49]. Further, in our studies, *MGMT* promoter methylation was shown to be partially reversible after eradication of *H. pylori* infection[49]. Overall, our studies indicate that MGMT-dependent DNA repair is disrupted during *H. pylori* gastritis, likely contributing to higher levels of mutagenesis in *H. pylori* infected gastric mucosa[49].

The nucleotide alterations introduced by 8OHdG, a marker of oxidative DNA stress, are G/C to T/A transversions, and in earlier studies we demonstrated that these were the most common type of point mutations induced by *H. pylori* in a co-culture setting[66], thus indicating that oxidative stress similar to that induced by inflammatory mediators can be replicated by *H. pylori* interacting with epithelial cells even in the absence of inflammation. If DNA repair is effective, the mismatch U:G caused by the 8OHG modification would be recognized by uracyl-DNA glycosylase or MSH2/MSH6 heterodimer and repaired. If DNA

repair is not effective then these mutations are expected to accumulate, consistent with our studies showing impaired DNA repair associated with *H. pylori* infection[49, 66, 67, 82]. In addition other studies have shown that enhanced and aberrant activity of activation-induced cytidine daminase (AID) in gastric epithelium in the setting of *H. pylori* infection can lead to increased U:G mismatches further contributing to the number of unrepaired mismatches and increased T/A transitions[28](Figure 1). Gene targets of AID enhanced mutagenesis in gastric cells include *TP53, CDKN-2B-CDKN-2A* (encoding p16, p15 and p14 suppressor proteins), and caused submicroscopic deletions with chromosome copy number losses involving the *CDKN-2B-CDKN-2A* locus[28, 83].

Epigenetic Gene Regulation and *H. pylori* Associated Gastric Carcinogenesis

Epigenetic DNA modifications are inherited upon somatic cell replication and encompass CpG methylation and histone modifications. Methylation of CpG islands in promoter regions causes silencing of the downstream gene, whereas methylation within the coding region of a gene usually is associated with increased gene transcription. Cancers display regional hypermethylation of promoter regions and global hypomethylation. The extensive epigenetic alteration in the background mucosa that gives rise to dysplasia and cancers represents an epigenetic field defect in inflammation and infection associated cancers. CpG methylation occurs early in gastric carcinogenesis, affecting genes such as *MLH* 1, p14, p15, p16, E-cadherin, *RUNX3*, thromobospondin-1 (*THBS1*), tissue inhibitor of metalloproteinase 3 *(TIMP-3), COX-2*, and *MGMT*[6, 16, 84–88]. Methylation of these and a number of other genes is associated with chronic inflammation in the gastric mucosa[89]. Pro-inflammatory interleukin-1-beta polymorphisms were shown to be associated with CpG island methylation of target genes such as the E-cadherin gene[90]. CpG methylation of the gastric mucosa has been shown to be partially reversible after eradication of *H. pylori* infection, supporting the notion that *H. pylori* and inflammatory mediators interfere with cellular mechanisms governing epigenetic regulation in gastric epithelium[17, 17, 49, 91].

Role of MicroRNAs in *H. pylori* Associated Gastric Carcinogenesis

MicroRNAs have been shown to be involved in *H. pylori* associated diseases[92]. Increased expression of miR-21 was detected in *H. pylori*-infected gastric mucosa, as compared to noninfected tissue[93], while *miR-218-2 and miR7* were down-regulated[94, 95]. *MicroR-204* downregulation was involved in aberrant Ras activation in gastric carcinogenesis[96]. *MiR-155* may function as a negative regulator that helps fine-tune the inflammation response of *H. pylori* infection[97].

Conclusions

New insights into the mechanisms through which *H. pylori* and mucosal inflammation lead to gastric cancer development have been unraveled in recent years. *H. pylori* virulence factors, in particular specific genotypes of *CagA* gene and *VacA* genes are important in carcinogenesis. Additional evidence has shown the role of chronic *H. pylori* infection in deregulation of epigenetic and microRNA molecular patterns and massively parallel sequencing has enabled the mutational mapping of gastric cancers, pointing to possible new candidate genes that may be evaluated next for a driver role in *H. pylori* and inflammation associated carcinogenesis. Mutation of the epithelial cell genome, a hallmark of cancer, has been demonstrated to accumulate in the gastric epithelium of *H. pylori* infected patients, through mechanisms that include active mutation burden in a milieu contaminated with oxygen radicals and the inability of adequate DNA repair that occurs during *H. pylori* infection. Stem cells of the stomach have been shown to be targets of oxidative damage in

the Helicobacter-inflammatory environment. Future research taking advantage of massively parallel sequencing genomic technologies, integrated systems biology and computational approaches are promising new tools to advance our understanding of how *H. pylori* and the consequent inflammation ultimately induce cancer in a sub-population of infected patients. Molecular markers that can identify patients with a history of *H. pylori* infection and associate with significant risk of development of GC remain a major goal of research, as are predictive markers for GC prognosis, targeted therapies, and recurrence. Identification of potential combinatorial biomarkers based on the bacterial genotypes, inflammation, and host genetic and phenotypic profiles should provide much needed tools for screening, prevention, and treatment of gastric cancer and precursor lesions.

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•• Of major importance

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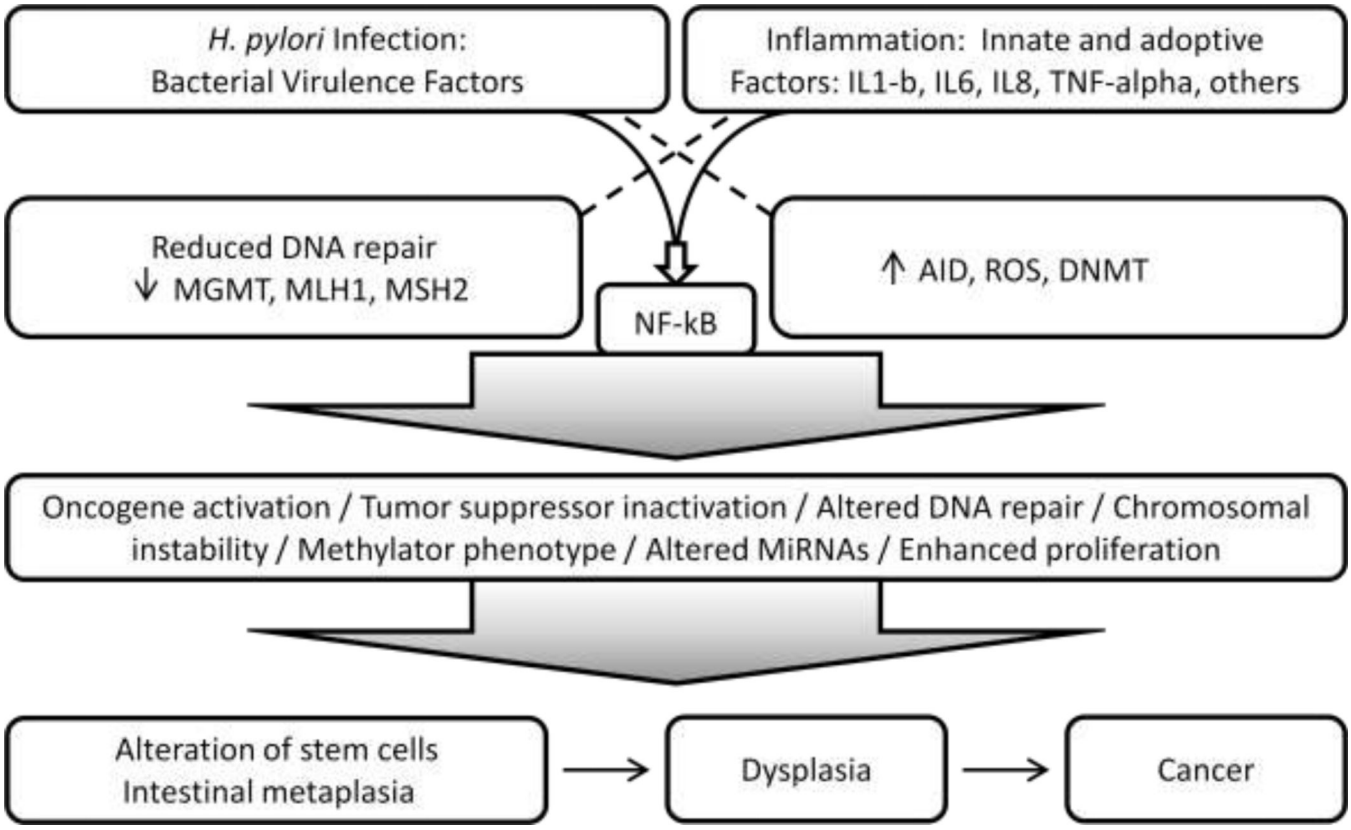

Figure 1.
H. pylori virulence factors and inflammation mechanisms leading to gastric cancer.