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Mitochondrial Stress in *Helicobacter pylori*-Associated Malignancies: A Review

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Mitochondrial Stress in *Helicobacter pylori*-Associated Malignancies: A Review

Viola Varga [1,†], András Gelley [2,†], Éva Margittai [1], Buket Bagci [3], Edina Wappler [4] and Ibolya Czegle [5,*]

[1] Institute of Translational Medicine, Semmelweis University, Budapest, Hungary
[2] Center of Internal Medicine, Buda Hospital of the Hospitaller Order of Saint John of God, Budapest, Hungary
[3] Department of Pathology, University of Rochester Medical Center, Rochester, New York, USA
[4] Department of Pathology and Laboratory Medicine, Boston University School of Medicine, Boston, MA
[5] Department of Internal Medicine and Hematology, Semmelweis University, Budapest, Hungary
* Correspondence: czegle.ibolya@semmelweis.hu
† These authors contributed equally to this work.

Abstract

Helicobacter pylori (H. pylori) infection is recognized as one of the most common bacterial infections worldwide. Its role in infection-associated cancers, such as in gastric cancer and MALT-lymphoma, is well known. Mitochondrial alterations in these malignancies are less documented. Mitochondria is a key organelle in maintaining cellular homeostasis under normal and pathological conditions. They regulate complex cellular processes, and they are key players in carcinogenesis and cancer progression in these *H.pylori*-associated malignancies. In this review, we summarize the role of mitochondrial stress in *H. pylori* infection, in gastric cancer, and MALT-lymphoma.

Keywords: *Helicobacter pylori*; mitochondrial stress; gastric cancer; MALT-lymphoma

1. General Aspects of Helicobacter Pylori Associated Malignancies

Helicobacter pylori (H. pylori) is a spiral shaped bacterium, first identified by Robin Warren and Barry Marshall in 1982 [1]. It is recognized as one of the most common bacterial infections worldwide, affecting over 50% of the global population [2]. This gram-negative bacterium specifically colonizes the gastric mucosa, as it is highly adapted to survive in this acidic environment. Recent comprehensive analyses showed that the global prevalence of *H. pylori* infection slightly decreased over the last few decades due to advances in hygiene in the developing countries, with the prevalence in adults being ~43.9% by 2022 from ~52.6% in 2015. In children and adolescents, however, the prevalence of *H. pylori* infection has not significantly decreased in any of the World Health Organizations- monitored region [3]. Its role in gastrointestinal diseases and cancer makes it a significant public health concern: long-term infection with *H. pylori* is a well-established risk factor for gastric cancer and for mucosa-associated lymphoid tissue (MALT) lymphoma. Clinically, *H. pylori* infection can be asymptomatic-particularly in the early stages of the infection, but it can also mimic peptic ulcer disease. In advanced stages, patients may present with dysphagia, weight loss, vomiting, or anemia. The gold-standard method for diagnosis is a microscopic examination of gastric biopsy specimens.

Gastric cancer remains the third most common cause of cancer-related mortality worldwide, with an estimated 1 million new cases each year [4], although its incidence has been declining. It is estimated that about 75% of all distal gastric adenocarcinoma are attributed to *H. pylori* infection. The other well-known cancer type induced by *H. pylori* is MALT lymphoma, arising from gastric

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lymphocytes. It has a lower incidence rate than gastric cancer, and eradication therapy leads to disease remission in 70% of early-stage cases [5].

Generally, *H. pylori* infection leads to chronic inflammation of the gastric mucosa, which has a pivotal role in the progression to the previously mentioned malignancies. *H. pylori* infection often decreases gastric acid production by modifying parietal cell function, resulting in an altered gastric pH environment that facilitates bacterial colonization and mucosal injury [6]. The *H. pylori*- induced inflammatory environment subsequently promotes genetic and epigenetic changes in gastric epithelial cells, contributing to neoplastic transformation. Additionally, *H. pylori* virulence factors, such as cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA) disrupt normal cellular processes and enhance carcinogenesis. Besides affecting epithelial cells, *H. pylori* exert various effects on immune cells, such as neutrophils, macrophages, dendritic cells, and lymphocytes, leading to the release of pro-inflammatory cytokines and chemokines that recruit and further activate immune cells, amplifying the inflammatory response in the gastric mucosa. This augmented activation and proliferation of mucosal B cells can lead to DNA mutations, eventually leading to lymphomatous transformation [7]

Targeting mitochondrial homeostasis pathways has emerged as a promising therapeutic strategy in both H. pylori- associated malignancies [8]. Restoration of balanced mitochondrial dynamics, mitophagy induction, or disruption of cancer-specific mitochondrial metabolism have shown potential in preclinical studies to improve treatment efficacy. This review summarizes our current understanding of mitochondrial equilibrium mechanisms in *H. pylori*-induced gastric adenocarcinoma and MALT lymphoma.

1.2. Pathological Classification of Helicobacter Pylori Associated Malignancies

1.2.1. Gastric Cancer

Gastric adenocarcinoma (gastric cancer [GC]) ranks as the 3-4th leading cause of cancer mortality worldwide, with approximately 1 million new cases, and 769,000 deaths annually [4] . Over 90% of cases occur in developing regions, where five-year survival remains below 30% due to late-stage diagnosis: more than 80% of patients present with advanced (stage III/IV) disease, when curative resection is no longer feasible. Early detection through endoscopy achieves >95% five-year survival, highlighting the need for effective screening and biomarker strategies.

GC can generally be classified as one of two epidemiologically distinct types: cardiac (upper gastric area) and non-cardiac (lower gastric area). *H. pylori* infection precedes approximately 89% of non-cardia GC cases. Chronic gastritis is a very common hallmark of *H. pylori* infection, with only 1-3% of cases progressing to atrophy, intestinal metaplasia, dysplasia, and to invasive adenocarcinoma, typically over decades [9].

In 1965, Lauren classified GCs into 2 major histological types, such as intestinal and diffuse type gastric adenocarcinoma. *H. pylori* infection has been associated with both. The intestinal type of gastric adenocarcinoma typically appears as a distinct polypoid mass, whereas the diffuse-type gastric adenocarcinoma presents as thickened stomach wall without a discrete mass. Since Lauren's original classification, multiple additional classifications have been proposed, including the Japanese classification of gastric carcinoma, the WHO classification, and those of Nakamura and colleagues, Ming, Mulligan, and Carneiro and colleagues. The most recent classifications by WHO (2019) and the Japanese classification of GC (2017) recognize the following five subtypes of GC: tubular, papillary, poorly cohesive, mucinous, and mixed adenocarcinomas.

The progression follows the Correa cascade, which is a well-established model describing the multistep process starting with chronic active gastritis, moving through multifocal atrophic gastritis (AG), then intestinal metaplasia (IM), dysplasia (abnormal cell growth), and finally invasive gastric adenocarcinoma. The most common tubular adenocarcinoma subtype is characterized by variably sized tubular structures, although solid areas may be present. Papillary adenocarcinoma demonstrates an exophytic growth pattern with elongated, finger-like projections. Poorly cohesive

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carcinoma, including signet-ring cell carcinoma, consists of neoplastic cells that may be arranged in small clusters, or can be found as isolated single cells with eccentrically placed nuclei and abundant intracytoplasmic mucin. Mucinous adenocarcinoma is defined by malignant epithelial cells embedded in extracellular mucin, comprising more than 50% of the tumor area. Lastly, mixed adenocarcinomas exhibit two or more distinct histological components.

The therapeutic approach depends on the stage of the disease; for GC, surgical resection combined with chemotherapy is generally the primary treatment option. Importantly, *H. pylori* eradication with antibiotics reduces GC risk by 30-50% in infected individuals, establishing it as the only modifiable carcinogen in its pathogenesis. Importantly, eradication therapy only is beneficial in the atrophic gastritis state, but it is no longer efficient in patients with metaplasia or dysplasia.

The 5-year survival rate is 70-95% in early stages (I-II) GC, dropping dramatically in advanced (III-IV) stages to only 5-25%. Metastatic cancer patients have a low overall survival time of 6-13 months. Finding reliable early-stage biomarkers are highly desirable to identify high-risk patients to detect the progression of chronic inflammation to adenocarcinoma [10].

1.2.2. MALT Lymphoma

MALT lymphoma is classified as an extranodal marginal zone lymphoma (EMZL) according to the 2016 revision of the WHO classification, with stomach being the most commonly affected organ, and accounting for 5- 8% of all B-cell lymphomas [11]. MALT lymphoma is a low-grade malignant B-cell lymphoma, which has an indolent clinical and biological behavioral pattern. [12]. It primarily affects adults over 60 years of age with a slight female predominance [13].

To date, *H. pylori* infection is considered the major trigger in the development of gastric MALT lymphoma in ~80% of cases [14]. The infection often leads to chronic inflammation accompanied with constant stimulation of the immune cells in the gastric mucosa, with subsequent B-lymphocyte activation and proliferation, which can eventually lead to neoplastic transformation [15]. *H. pylori* eradication has been shown to induce lymphoma remission in ~80% of patients.[16] Since the widespread use of *H. pylori* antibiotic therapy, the incidence of *H. pylori*- positive gastric EMZL has declined; however, the incidence of *H. pylori* -negative gastric EMZL appears to be increasing, potentially due to involvement of other *Helicobacter* species. [17] [18]

The diagnosis of MALT lymphoma involves endoscopic biopsy with histological and immunohistochemical analysis [19]. Treatment often begins with *H. pylori* infection eradication, using antibiotics, which can result in tumor regression in up to 70% of cases of early-stage gastric MALT lymphoma [19] [20] [21] [22] [23] [24]. For *H. pylori*-negative cases and more advanced disease, other therapeutic options, such as radiotherapy, chemotherapy, or targeted therapies are used, with an excellent prognosis in early-stage MALT- lymphoms [24] [25].

Clinically, patients may be asymptomatic or may present with symptoms related to mass effect. Symptoms are often nonspecific, including fatigue, nausea, weight loss, and abdominal discomfort in gastric involvement [26]. Severe features can include chronic gastrointestinal bleeding, anemia, or pyloric obstruction. Advanced stages are uncommon, but may involve systemic dissemination to lymph nodes, liver, or to the bone marrow [25].

Microscopically, EMZL shows a proliferation of small to medium-sized lymphoid cells that efface the gastric architecture, infiltrating and distorting epithelial structures. The hyperplastic lymphoid follicles may be colonized by neoplastic cells, resulting in a nodular appearance. The neoplastic population consists of centrocyte-like cells with small to medium size, slightly irregular nuclei, smooth chromatin and pale cytoplasm. Dutcher bodies and Russell bodies may also be observed. The neoplastic cells express CD19, CD20, Pax5, CD79a and BCL2. Aberrant expression of CD43 and immunoglobulin light chain restriction support the diagnosis. EMZL are typically negative for CD5, CD10, BCL6, and CD23. The Ki67 proliferation marker is typically low, but it may be focally high in residual germinal centers. Furthermore, CD21 staining can highlight expanded follicular dendritic cell meshwork [25].

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1.2. Introduction to Classical Molecular Mechanisms of H. pylori-Driven Carcinogenesis

1.2.1. Gastric Cancer

Although *H. pylori* was discovered in 1982, it wasn't until 1994 that it was classified as class 1 carcinogen by the WHO. The discovery of the role of *H. pylori* was highly significant, as it not only identified the etiologic agent, but also enabled effective treatment. Although several mechanisms have been proposed, its exact pathogenesis still remains incompletely understood. The bacterium's complex genomic plasticity, geographic variation and the involvement of multiple virulence-related genes made it difficult to establish one definitive pathogenetic pathway.

The Cag pathogenicity island (cagPAI) and cytotoxin-associated gene A (Cag A) play an important role in gastric carcinogenesis. The cagPAI encodes type IV secretion system and effector protein CagA [27]. Type 4 secretion system functions as translocation apparatus that delivers CagA into epithelial cells during bacterial adherence. Once internalized, CagA is phosphorylated at its glutamate-proline-isoleucine-tyrosine-alanine (EPIYA) motifs by host kinases c-Src and c-Abl [28]. In East Asian populations, EPIYA-D motif exhibits higher binding affinity, leading to more pronounced pathogenetic effects [29]. Phosphorylated CagA binds to host tyrosine phosphatase, resulting in activation of the RAS-ERK/MAPK pathway and promoting uncontrolled cell proliferation, cytoskeletal rearrangements, increased inflammation, enhanced permeability and disruption of epithelial barrier integrity. In addition, CagA contributes to carcinogenesis by inhibiting apoptosis.

Vacuolating cytotoxin A (VacA), a pore-forming toxin secreted by *H. pylori*, induces causes the vacuolization in host cells and modulates T cell proliferation, mitochondrial function, apoptosis, interleukin-8 (IL-8) production and ultimately promoting autophagy [30]. Other bacterial factors, including urease and flagella, further enhance survival and pathogenicity by neutralizing gastric acidity and facilitating colonization and adherence [31]. Urease also stimulate IL-8 production, amplifying local inflammation and the host immune response [30].

H. pylori induces several major molecular mechanisms that contribute to gastric carcinogenesis. One major pathway involves sustained STAT3 activation via IL-6 upregulation, CagA mediated signaling through SHP2 and stimulation of Toll-like receptor 2. Downstream effects, including DAB2 overexpression through the SRC–YAP1 pathway and FGFR4 induction further amplify oncogenic signaling. Collectively, persistent STAT3 activation drives cell proliferation, survival and inflammation, underscoring its central role in Helicobacter pylori–associated gastric cancer.

NF-κB is another key transcription factor in *H. pylori*- associated GC tumorigenesis. *H. pylori* activates NF-κB through several mechanisms, including direct activation by CagA, stimulation of the IKK complex, and induction of pro-inflammatory cytokines such as tumor necrosis factor-alpha and interleukin-1β. NF-κB amplifies inflammation through positive feedback loops and promotes oncogenesis by upregulating factors such as HNF4α, PRDX2, CDX2, and components of the PIEZO1–YAP1–CTGF and RASAL2–β-catenin pathways [32] . Through these interactions, NF-κB enhances cell proliferation, inhibits apoptosis, promotes angiogenesis, and cooperates with other pathways such as STAT3 and HIF-1α to support tumor progression. [33] [34]

The Wnt/β-catenin signaling pathway is another driver of *H. pylori*– associated gastric carcinogenesis. *H. pylori*, particularly through CagA, promotes β-catenin accumulation and nuclear translocation by mechanisms such as CagA–LRP8 interactions and ASCL1-mediated AQP5 induction, thereby activating genes involved in cell cycle progression, stem cell renewal, and inhibition of apoptosis. [35] [36] Sustained β-catenin activity also facilitates epithelial–mesenchymal transition, enhancing tumor cell motility and invasiveness. [37] In addition, Wnt/β-catenin signaling interacts with other oncogenic pathways—including NF-κB and YAP—creating a synergistic network that accelerates malignant transformation. Overall, persistent activation of this pathway represents a critical mechanism through which *H. pylori* drives both the initiation and progression of gastric cancer. Other pathways, including the mitogen activated protein kinase pathway, the hippo pathway and PIK3K/Akt pathway also contribute to the development *H. pylori*- associated GC [38].

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1.2.2. MALT Lymphoma

The neoplastic cells in EMZL correspond to post-germinal center memory B cells that remain responsive to signals delivered through CD40 ligand on activated T cells and to cytokines released by antigen-stimulated T helper cells. In vitro studies demonstrate that these neoplastic cells require CD40 signaling and Th2 type cytokines for cell proliferation and differentiation.[39] Under conditions of chronic antigenic stimulation such as *H. pylori* infection or autoimmune disorders, ongoing immune activation creates a microenvironment conducive to lymphomagenesis. Activated T cells and recruited neutrophils produce abundant cytokines and reactive oxygen species (ROS), promoting continuous activation and expansion of peripheral B lymphocytes. This inflammatory milieu enhances signaling through Toll-like receptors, the B-cell receptor, and B-cell-activating factor, resulting in sustained NF-κB activation. Concurrently, ROS-induced DNA injury increases the likelihood of genetic alterations.

Among these genetic events, the t(11;18)(q21;q21)/BIRC3::MALT1 fusion is particularly notable, and this alteration is associated with the presence of CagA- positive *H. pylori* strains. [40] This translocation, found in approximately 24% of gastric EMZLs, results in a BIRC3::MALT1 fusion protein capable of activating both the canonical and non-canonical NF-κB pathways, thereby promoting lymphomagenesis and resistance to *H. pylori* eradication therapy [40] [41]. The chromosomal translocation t(1;14)(p22;q32) is found in about 5% of MALT lymphomas, resulting in dysregulated BCL10 expression, a protein that directly connects antigen receptor signaling to the NFκB pathway [42] [43]. In MALT lymphomas carrying this mutation, BCL10 is strongly expressed in both the nucleus and cytoplasm, whereas in normal germinal center B cells, its expression is weak and largely restricted to the cytoplasm [44]. Over time, the accumulation of these molecular alterations, and others, can drive the transformation of chronically stimulated B cells into an extranodal marginal zone lymphoma (EMZL) phenotype.

2. H. pylori Infection and Mitochondrial Stress

The maintenance of mitochondrial homeostasis is ensured by tightly regulated mechanisms. Their major role is in energy production via oxidative phosphorylation (OXPHOS) through the mitochondrial electron transport chain, providing ATP to the cell. Beyond energy production, mitochondria regulate several vital cellular processes, including the ROS production, calcium homeostasis, synthesis of key molecules, and initiation of apoptosis. Mitochondria have their own circular DNA (mtDNA) and they can replicate independently within the cell. To maintain mitochondrial quality control there are special mechanisms; they have mtDNA repairing enzymes (mtBER, mismatch repair, POLG) and mitochondrial dynamics—fusion and fission—along with mitophagy that can prevent the accumulation of dysfunctional mitochondria. The balance of mitochondrial fusion and fission is crucial for mitochondrial homeostasis, cell stability and survival. Fusion is important for repairing damaged mitochondria, while fission can activate mitophagy to induce mitochondrial clearance. Their role is indispensable for adapting to cellular energy demands, regulating apoptosis, and controlling oxidative stress.

Disruption of mitochondrial homeostasis by *H. pylori* infection plays a central role in the metabolic reprogramming of cancer cells, evasion of apoptosis, enhanced proliferative capacity, and increased metastatic potential [45]. The infection induces shifts from OXPHOS toward glycolysis, supporting the high proliferative and metastatic potential of gastric epithelial cells. *H. pylori* is also responsible for causing mutations in mtDNA, which have been demonstrated to exacerbate mitochondrial dysfunction, to increase ROS production, and to contribute to its tumorigenic potential [46]. These mtDNA mutations impair mitochondrial replication and transcription, aggravating energy deficits.

Alterations in mitochondrial dynamics is a hallmark for *H. pylori* infection, characterized by increased fission and reduced fusion that have been associated with decreased apoptosis [47] [48]. Furthermore, impairment of mitophagy leads to the accumulation of damaged mitochondria,

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promoting oxidative stress increasing the inflammatory signaling, contributing to tumor progression [49]. (Figure 1).

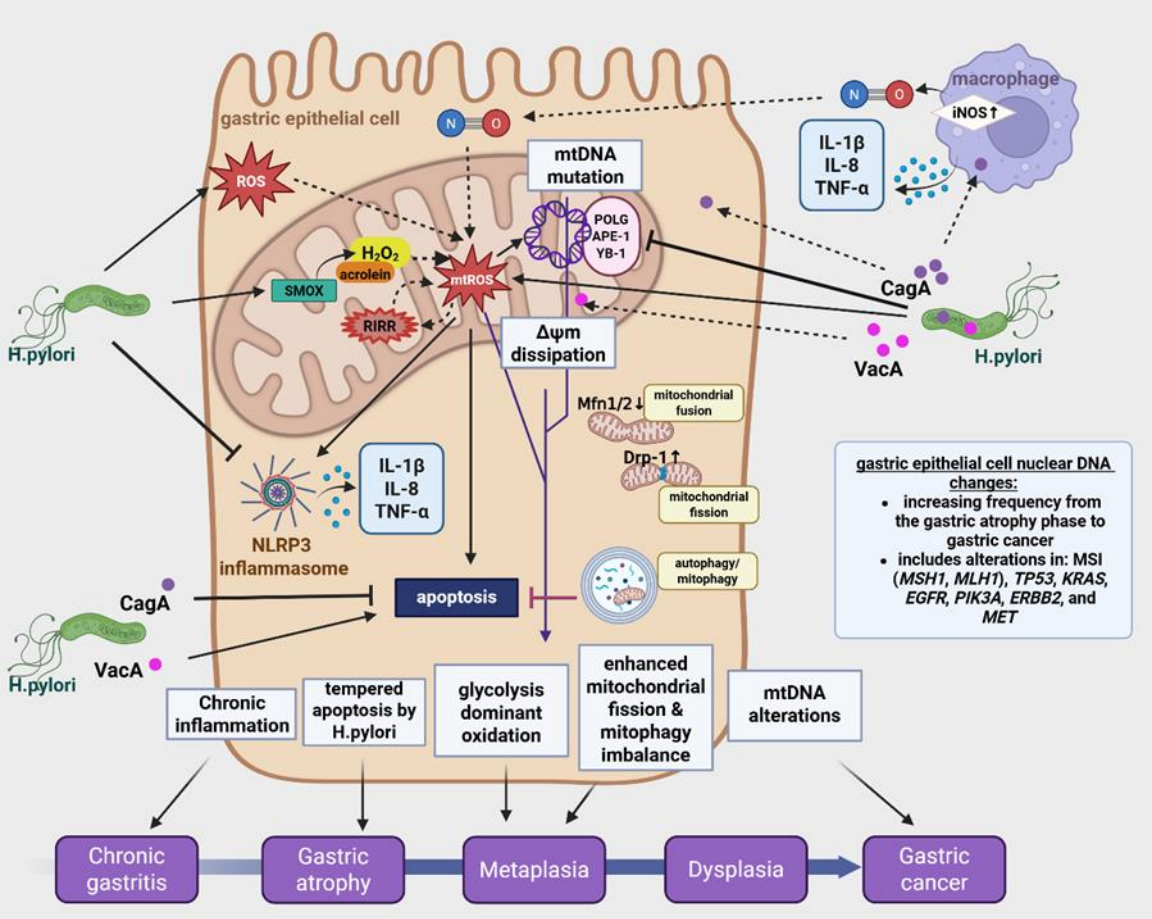

Figure 1. Helicobacter pylori infection induces multifaceted pathological changes in gastric epithelial cells , many of which are mediated via mitochondrial-related pathways. H.pylori mediates most of its pathogenic effects through its virulence factors, with CagA and VacA being the most crucial. VacA forms an anion-selective channel in the inner mitochondrial membrane, resulting in dissipation of the mitochondrial membrane potential (Δψm). In addition, *H. pylori* upregulates spermine oxidase (SMOX) generating H2O2 and acrolein as a byproduct. Reactive oxygen species (ROS) coming from multiple pathways from the cytoplasm together with excessive mitochondrial ROS (mtROS) production, triggering ROS-induced ROS release (RIRR), amplifying oxidative stress. Eventually, mtROS leads to mtDNA mutations, enhancing the needs for DNA repair mechanisms, such as BER or mismatch repair. However, key enzymes of DNA repair (APE-1, YB-1 and POLG) are altered upon *H.pylori* infection, which exacerbates mitochondrial DNA instability.

These insults activate mitochondrial quality control pathways, including mitochondrial dynamics (fusion and fission) and mitophagy. The persistent infection and chronic inflammation will eventually favor mitochondrial fission and induce mitophagy. In later stages of the infection, these pathways will be not sufficient, and dysfunctional mitochondria will be accumulated.

In addition, mitochondrial dysfunction promotes NLRP3 inflammasome activation and release of inflammatory cytokines (such as IL 1β, IL 8, and TNF α), sustaining chronic inflammation in both epithelial and immune (B-) cells. Furthermore, CagA induces iNOS expression in immune cells (such as macrophages), leading to increased production of nitric oxide (NO) that also form other reactive nitrogen species (RNS), which in turn activate downstream inflammatory signaling pathways.

These mitochondrial and inflammatory perturbations converge to drive cellular transformation and metaplastic progression. In gastric epithelial cells, multiple mitochondrial quality-control pathways are initially activated in response to H. pylori infection; however, when ROS production

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exceeds these compensatory defenses, mitochondria typically trigger apoptosis, often associated with excessive mitochondrial fission. At the same time, H. pylori can dampen NLRP3 inflammasome activation to support cell survival, while promoting a shift from OXPHOS to glycolysis, and fostering the accumulation of mtDNA mutations. Taken together, these interconnected processes steer gastric epithelial cells toward metaplasia and dysplasia, ultimately facilitating malignant transformation during persistent H. pylori infection. The image shows the earliest effect of mitochondria- associated changes in the relation to the different stages of gastric cancer development. Note that most of those changes are present in the later stages of this process (arrows only showing the initial impacts).

Although nuclear DNA alterations are not shown in the gastric epithelial cell on this image, it is crucial in the development of gastric cancer, and it is summarized in a vignette on the right side of the image.

Solid standard arrow: induction/activation; Solid blunt/T-bar arrow: blocking/inhibition; Dashed line: translocation.

Created in BioRender. Wappler-Guzzetta, EA. (2025) https://app.biorender.com/illustrations/6933475960be5c067831d4c8?slideId=7af0b0df-ca50-421a-88a5-9c1f3fa1cd5b (accessed on 12/12/2025)

2.1. H. pylori Infection on the Mitochondrial Functions of Gastric Epithelial Cells

H. pylori colonizes the mucosal surface using virulence factors to disrupt cellular signaling and integrity, leading to impaired epithelial barrier function. The impairment of cellular integrity is primarily mediated through disruption of the tight junctions and adherens junctions, which eventually leads to decreased transepithelial electrical resistance (TEER), reflecting increased epithelial permeability [50]. Disruption of the epithelial barrier compromises its protective function, facilitating the translocation of luminal contents such as acid, pepsin, and microbial products as well as any pathogens (*H. pylori* itself) into the lamina propria, which exacerbates mucosal inflammation and injury [51]. Bacterial penetration potentially damaging the extracellular matrix structure of lamina propria that impairs epithelial regeneration and disrupts tissue architecture, contributing to chronic gastritis and increasing the risk for ulceration and neoplastic transformation [52]. These changes in the microenvironment initiate many intracellular signaling, which can lead to mitochondrial dysfunction and predispose the cells to neoplastic transformations. (Figure 1.)

2.2. Molecular Mechanisms of Virulence Factors

H. pylori is a highly adapted bacterium that possesses a wide repertoire of virulence factors essential for its survival, colonization, and pathogenesis within the harsh acidic environment of the stomach. These virulence determinants include urease, which neutralizes gastric acid; flagella and associated motility proteins (FlaA, FlaB) that facilitate penetration through the mucus layer; adhesins such as BabA, SabA, OipA, and HopQ which mediate attachment to gastric epithelial cells; the neutrophil-activating protein (Hp-NAP) that modulates immune responses; lipopolysaccharides (LPS) that mimic host molecules; the cag pathogenicity island (cagPAI) encoding the type IV secretion system (T4SS) and its effector protein CagA; the vacuolating cytotoxin A (VacA); γ-glutamyl transpeptidase (GGT); and various enzymes including phospholipases and antioxidants such as catalase and superoxide dismutase which help the bacterium survive oxidative stress [53] [54] [55].

Among these, VacA and CagA stand out as the most critical virulence factors for inducing mitochondrial dysfunction due to their direct translocation into host cells and specific targeting of mitochondrial homeostasis. Virtually all *H. pylori* strains produce VacA, a secreted pore-forming toxin that permeabilizes mitochondrial membranes, whereas CagA is expressed in ~60-70% of strains harboring the cagPAI, and is injected via T4SS, modulating mitochondrial dynamics and mitophagy [56] [57] [58].

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2.2.1. Vacuolating Cytotoxin A (VacA)

The Vacuolating cytotoxin A (VacA) of *H. pylori* is a key factor responsible for inducing pronounced vacuolization in host cells. Upon binding to the cell surface, VacA is internalized and causes the formation of large intracellular vacuoles, which display characteristics of both late endosomes and early lysosomes. This vacuolization results primarily from VacA forming anion-selective channels in the membranes of these vesicles, leading to the accumulation of chloride ions and subsequent osmotic swelling. Although in *in vitro* experiment this vacuolation is very severe in the human stomach it is less prominent [59]. However, beyond inducing vacuolation, it has become increasingly evident that VacA also exerts direct effects on mitochondrial function, further contributing to cellular injury and apoptosis [60].

VacA is synthesized as a ~140 kDa protoxin, proteolytically processed into p33 (N-terminal) and p55 (C-terminal) subunits that remain non-covalently associated. The N-terminal hydrophobic domain of p33 appears critical for its mitochondrial targeting and membrane insertion, likely allowing the protein to engage the translocase of the outer membrane (TOM) complex at the outer membrane and, subsequently, a translocase of the inner membrane (TIM) complex at the inner membrane, analogous to canonical presequence- or carrier-dependent import pathways [61,62,63].

The p55 domain is primarily responsible for host cell receptor binding—interacting with RPTPβ/α, lipid rafts, and sphingomyelin—and facilitating endocytosis. Earlier studies suggested that the p33 subunit, but not the p55 subunit of VacA, could enter mitochondria to modulate organelle function [64]. Crystallography studies revealed that both subunits are required for a physiologically stable pore and p55 mediates initial oligomerization between adjacent subunits, forming flower-like hexadecameric or dodecameric assemblies upon acidification, which is essential for membrane insertion [65]. Reconstitution experiments demonstrate that independently expressed recombinant p33 and p55 can reassemble into functional oligomers, restoring vacuolating and channel-forming activities, confirming their interdependent roles [66].

VacA exhibits significant allelic polymorphism that profoundly influences its toxicity, cellular tropism, and disease association [67]. The vacA gene is mosaic-structured and categorized into three main variable regions: the signal sequence (s1/s2), mid-region (m1/m2), and intermediate region (i1/i2). The s1/m1 (especially s1/i1/m1) combination is recognized as the most pathogenic, strongly correlating with peptic ulceration (OR 2-4), gastric atrophy, and adenocarcinoma risk (up to 5-fold higher, then other strains) [68] [69]. The s1/m1 strains produce higher levels of vacuolating activity and exhibit enhanced cellular tropism compared to s2 or m2 variants[70]. In contrast, s2 or m2 variants show reduced toxicity: the s2 allele encodes an N-terminal hydrophilic extension that impairs channel formation, secretion, and membrane insertion, while m2 strains produce a truncated toxin with limited cellular tropism and vacuolating activity [71] [72]. These polymorphisms explain geographic disease variation—s1/m1 strains predominate in high-GC regions like East Asia—and synergize with cagA-positive strains to amplify mitochondrial stress and carcinogenesis [71].

Once localized to mitochondria, VacA assembles into oligomeric anion-selective channels, primarily permeable to chloride ions, within the inner membrane. It was calculated that even a single channel is capable of dissipating the mitochondrial membrane potential ($\Delta\psi m$), which is essential for ATP synthesis and mitochondrial homeostasis. This membrane potential dissipation triggers the release of pro-apoptotic factors, such as cytochrome c, activates Bax and Bcl-2 family proteins and caspase-9/3, culminating in intrinsic apoptosis [73] [64].

2.2.2. Cag Pathogenicity Island (cagPAI) and Cytotoxin-Associated Gene A (CagA)

Most *H. pylori* strains contain a ~40 kb gene cluster known as the cag pathogenicity island (cag PAI) and those strains containing the cag PAI show enhanced potential to induce mtROS and inflammation, correlating with increased virulence and gastric disease severity [56] [74].

The cag PAI contains about 30 to 31 genes, including cagA and multiple genes essential for the assembly and function of the type IV secretion system (T4SS), which is required for delivery of CagA into host cells. [54] [75] CagA comprises an N-terminal secretion domain (for T4SS recognition), three

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conserved arginine-rich regions (ARR1–3) facilitating plasma membrane binding to phosphatidylserine, a central multidomain region interacting with host effectors, and a variable C-terminal region harboring 1–10 Glu-Pro-Ile-Tyr-Ala (EPIYA) motifs [56]. After CagA translocate into the epithelial cell, it is phosphorylated at the EPIYA motifs by Src/Abl kinases, which enables its interaction with the SRC homology 2 domain (SH2)-containing tyrosine phosphatase SHP-2 [76] [77] [78].

EPIYA motifs are classified as A, B, C and D type [43]. While A and B are ubiquitously expressed, in Western countries *H. pylori* frequently contains the C type motif as well and most strains from the East Asian countries contains the D type motif [44]. Interestingly, strains carrying EPIYA-D are associated with higher risk of gastric cancer due to enhanced binding affinity with SHP-2 [79]. They also demonstrate more prominent alteration of intracellular signaling inducing severe hypoxia and high level of ROS. However, an additional EPIYA-C motif can also induce the transcription of host genes involved in gastric cancer progression, such as erbB2, HGF-R, FGFR4 and TGF-ß [80].

The *H. pylori* oncoprotein CagA interacts with the SH2 domain-containing inositol 5-phosphatase 2 (SHIP2, INPPL1), a lipid phosphatase that hydrolyzes phosphatidylinositol 3,4,5-trisphosphate [PI(3,4,5)P_3] to phosphatidylinositol 3,4-bisphosphate [PI(3,4)P_2], thereby modulating actin cytoskeleton dynamics, cell migration, and adhesion [81]. This interaction occurs in a tyrosine phosphorylation-dependent manner at CagA's C-terminal EPIYA motifs: Western-type CagA (EPIYA-C) binds SHIP2 more avidly than East Asian-type CagA (EPIYA-D), though both subtypes engage the SH2 domain of SHIP2 following Src/Abl kinase-mediated phosphorylation post-T4SS translocation [82].

Upon binding, CagA tethers SHIP2 to the plasma membrane via its N-terminal lipid-binding motifs, elevating local PI(3,4)P_2 levels. This phosphatidylinositol remodeling strengthens *H. pylori*-host cell attachment by enhancing integrin-mediated adhesion (via CagL-α5β1) and stabilizing bacterial microcolonies, thereby potentiating subsequent T4SS-mediated CagA delivery [83]. In SHIP2-knockout gastric epithelial cells (e.g., AGS), CagA delivery is significantly reduced, underscoring SHIP2's role in early infection dynamics.

The CagA-SHIP2 axis amplifies CagA's morphogenetic activity, including the "hummingbird phenotype" (epithelial-mesenchymal transition-like cell elongation and motility), which reflects enhanced invasiveness. By facilitating greater CagA influx, SHIP2 indirectly promotes downstream oncogenic signaling through CagA-SHP2 complexes, Nuclear Factor of Activated T cells (NFAT) activation, and β-catenin stabilization, contributing to gastric carcinogenesis [47,48]. East Asian CagA variants, despite weaker SHIP2 affinity, exhibit higher overall oncogenicity, potentially due to stronger SHP2 binding compensating for reduced initial adhesion [56].

This sequential interplay—initial CagA-SHIP2 interaction boosting delivery, followed by CagA-SHP2-mediated transformation—represents a sophisticated "hit-and-run" strategy enabling persistent infection and malignant progression.

Multimerization motifs within the C-terminal region of the Helicobacter pylori CagA protein, known as CagA-multimerization (CM) motifs or CM-like sequences, are critical for its ability to self-associate (oligomerize) within host cells. These motifs consist of approximately 16 amino acid residues located immediately downstream of the last EPIYA phosphorylation segment. The CM motifs enable CagA to form dimers or higher-order oligomers independently of its phosphorylation status, which markedly enhances its biological activity [56] [84]. Structurally, CM motifs serve as interaction interfaces facilitating head-to-tail binding between CagA molecules, thereby stabilizing multimeric complexes. This multimerization significantly increases the strength of CagA's interactions with host signaling proteins, especially the SH2 domain-containing phosphatase SHP2, a critical mediator of CagA-driven oncogenic signaling pathways [85]. Quantitative analyses reveal that tandem repeats of CM motifs act synergistically, exponentially increasing CagA binding affinity for SHP2, which amplifies downstream effects such as aberrant cell morphology (the "hummingbird phenotype"), disrupted cell polarity, and enhanced proliferative signaling [84] [85].

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2.2.3. Interactions Between VacA and CagA

VacA and CagA exhibit functional antagonism in many ways. This "yin-yang" regulation sustain chronic non-lethal inflammation: acute VacA clears competitors, CagA drives transformation (SHP2/β-catenin), VacA sustains CagA for persistence. The CagA positive, vacAs1/m1 phenotypes correlate with higher GC/MALT prevalence.

Interestingly, CagA expression can inhibit VacA endocytosis and modify its cellular trafficking [86]. Co-infection with cagPAI-positive strains alters VacA subcellular localization, potentially enhancing its mitochondrial targeting efficiency through T4SS-mediated crosstalk or shared receptor utilization, thereby amplifying mitochondrial stress [60] [87]. However, phosphorylated CagA blocks VacA pinocytosis and endosomal maturation, reducing vacuolation by 40-60% in AGS cells.

Furthermore, VacA can induce the dissipation of mitochondrial membrane potential, cytochrome c release and apoptosis. CagA mediated PI3K/Akt activation NFAT nuclear translocation counteract these mechanisms. On the other hand, CagA-induced mitophagy clears VacA-damaged mitochondria, balancing ROS to prevent apoptosis while sustaining chronic stress. VacA can stabilize CagA levels by inhibiting CagA degradation. In case of VacA is absent, host mechanisms degrade 70% of injected CagA within 6h. VacA inhibition restores "hummingbird" morphology, and VacA's lipid raft disruption impairs lysosomal targeting of CagA. VacA reduces gluthation, sensitizing cells to H_2O_2, which is a byproduct during CagA induced SMOX activity. VacA and CagA are both responsible for higher RNS production. They also share NF-κB signaling pathways, CagA induces canonical, while VacA the non-canonical pathways, counterbalancing inflammation.

Table 1. Interactions between CagA and VacA, and their role in carcionogenesis.

NF-κB Level	$CagA^+VacA^+$	CagA-only	VacA-only	Pathogenic Outcome
p65/RelA (canonical)	Moderate ↑	High ↑↑↑	Low	Proliferation ✓
RelB/p52 (non-canonical)	Moderate ↑	Low	High ↑↑↑	Recruitment ✓
Total NF-κB activity	Optimal	Excessive(cell cycle arrest)	Ineffective (apoptosis)	Persistence✓

This cooperative toxicity explains higher disease risk in cagA+/s1m1 VacA strains

[88]. The coordinated mitochondrial targeting by VacA and CagA underscores *H. pylori*'s sophisticated manipulation of host cell metabolism, fostering persistence and disease progression. (Figure 1.)

2.3. VacA and CagA in ROS/RNS-Induced Oxidative Cascade

H. pylori can induce inflammation and oxidative stress through its virulence factors, triggering most adaptive and apoptotic pathways. The prominence of these pathways depends on the bacterial strain, the condition of the host cells and other environmental factors. However, mitochondria play a central role in most of these pathways, as they are the main source of intracellular ROS production.

In addition, VacA channel activity directly precipitates mitochondrial reactive oxygen species (mtROS) overproduction through electron transport chain (ETC) leakage and impaired glutathione metabolism following $\Delta\Psi m$ dissipation [89] [90] [91] [92].

VacA initiates ROS-induced ROS release (RIRR), a propagating mechanism wherein mtROS from one mitochondrion diffuses to adjacent organelles, eliciting synchronized Ca^{2+} waves and amplified ROS bursts that facilitate inter-mitochondrial communication [58].

Helicobacter pylori infection via CagA prominently induces the expression and activity of spermine oxidase (SMOX), a key enzyme involved in polyamine metabolism that catalyzes the

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conversion of spermine into spermidine, producing hydrogen peroxide (H_2O_2) as a reactive oxygen species byproduct [93]. Studies have demonstrated that the generation of H_2O_2 contributes to oxidative DNA damage, mucosal inflammation, and drives gastric epithelial cell apoptosis, thus playing a pivotal role in the pathogenesis of *H. pylori*-associated gastric cancer. A pilot study also confirmed the increased level of SMOX expression in gastric cancer patients with the history of *H. pylori* infection [94]. Genetic deletion or pharmacological inhibition of SMOX in animal models significantly reduces inflammation, oxidative DNA damage, and tumorigenic signaling, including suppression of β-catenin pathway activation, a key driver of oncogenesis in gastric tissues [95].

CagA also promotes iNOS expression in epithelial/immune cells via NF-κB/STAT3, generating NO- that forms peroxynitrite ($ONOO^-$) with superoxide [96].

This chronic oxidative/nitrosative stress overwhelm antioxidant defense systems (e.g., SOD2, glutathione, arginase) [90] [97], causing mtDNA damage, lipid peroxidation, protein carbonylation, and nitrotyrosine formation leading to carcinogenesis [98].

3. H. pylori Induces Mitochondrial Dynamics Imbalance

H. pylori infection significantly disrupts mitochondrial dynamics, contributing to gastric epithelial cell damage and pathogenesis. Presumably both VacA and CagA toxins can mediate mitochondrial fragmentation by recruiting dynamin-related protein 1 (Drp1), which is a key mediator of mitochondrial fission. Fission protein 1 (FIS1) is also necessary for mitochondrial fission as it serves as binding sites for Drp1 recruitment. CagA can increase the expression level of both Drp1 and FIS1 in human gastric cancer (AGS) cell line [99]. Mitofusins (MFN1 and MFN2) are GTPases located in the outer mitochondrial membrane that are essential for mitochondrial fusion. They facilitate the formation of connections between adjacent mitochondria, while the next step is mediated by optic atrophy 1 (OPA1) protein in the inner membrane of the mitochondria. Fusion is necessary for maintaining the integrity of the mitochondrial network, mixing the mitochondrial contents (e.g., mtDNA and proteins), and the functional complementation of damaged organelles. During CagA treatment both MFN1 and MFN2 expressions were decreased, indicating a decreased mitochondria fusion in the gastric cells [99]. This fragmentation disrupts mitochondrial dynamics, compromising mitochondrial network integrity and leads to decreased respiratory capacity and ATP production. Inhibition of Drp1 activity in VacA-exposed cells prevents activation of the pro-apoptotic protein Bax, mitochondrial outer membrane permeabilization (MOMP), and subsequent cell death, confirming mitochondrial fission as a central effector of VacA toxicity [100].

This mitochondrial fragmentation precedes cell death and highlights the critical role of altered mitochondrial morphology in *H. pylori*-induced cytotoxicity. Additionally, mitochondrial fusion and fission imbalance causes accumulation of damaged mitochondria, which triggers mitophagy as a quality control mechanism to remove dysfunctional organelles, thereby impacting cellular survival and inflammation [101] [102] . VacA-induced mitochondrial damage also activates metabolic stress pathways involving AMPK, which interplay with mitochondrial fission and autophagy to regulate toxin clearance and cell viability [101] [87]. These coordinated alterations in mitochondrial dynamics and quality control mechanisms help the bacterium maintain a chronic infection environment while driving pathogenesis through mitochondrial dysfunction [103] [104]. (Figure 1.)

4. Autophagy—Mitophagy

H. pylori infection triggers both autophagy and mitophagy as crucial host defense mechanisms to remove damaged mitochondria and dysfunctional cellular components. Vacuolating cytotoxin A (VacA) is a key inducer of both autophagy and mitophagy, promoting mitochondrial depolarization and stabilizing PINK1 on the outer mitochondrial membrane, which recruits Parkin for ubiquitination and LC3-mediated mitophagy [105] [106]. However, VacA also impairs this quality control by sustaining mitochondrial membrane potential ($\Delta\psi m$) perturbations, overwhelming

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mitophagic capacity and pushing the cell towards apoptosis when autophagic clearance is insufficient [107] [99].

In contrast to VacA, CagA has a complex regulatory role in mitochondrial quality control and inflammation during *H. pylori* infection. It promotes selective mitophagy via the PINK1/Parkin pathway, which leads to the removal of damaged mitochondria. This action attenuates excessive inflammation by preventing the overactivation of the NLRP3 inflammasome, thereby balancing inflammatory responses and helping the bacterium evade host immune clearance. By maintaining a controlled level of mitochondrial reactive oxygen species (mtROS), CagA supports chronic infection and increases the survival and viability of infected gastric epithelial cells [108] [99].

However, according to other studies CagA also activates NADPH oxidase (NOX) through ERK/NF-κB signaling, which enhances ROS production and promotes inflammation [109], while simultaneously inhibiting general autophagic flux through pathways such as c-Met-PI3K/Akt/mTOR pathway, promoting cell stress [108] [106]. (Figure 1.)

Chronic infection also suppresses autophagic degradation via downregulation of key regulators like SIRT1 and RUNX3, contributing to impaired cellular clearance and promoting pathological inflammation [107] [109]

Overall, the interplay between *H. pylori* virulence factors and host autophagic pathways represents a dynamic balance where autophagy/mitophagy attempts to mitigate mitochondrial damage and control inflammation, but *H. pylori* can influence these pathways in order to survive, however it may also lead to gastric disease progression.

5. Apoptosis

In cases, when mitophagy is insufficient to remove damaged mitochondria, *H. pylori* can induce apoptosis of gastric epithelial cells through both intrinsic and extrinsic pathways. VacA plays a major role in the initiation of apoptosis, while CagA can modulate, and in some extend counteract its effect.

H. pylori VacA primarily activates the intrinsic (mitochondrial) apoptotic pathway by generating ROS and DNA damage, upregulating BH3-only proteins such as Bim and PUMA and activating BAX and BAK, which, together with VacA, permeabilize the mitochondrial outer membrane, dissipate $\Delta\psi m$, and trigger cytochrome c release, leading to caspase-9 then caspase-3 activation and ultimately to apoptosis [110] [111]. VacA can also intersect with non-canonical forms of programmed cell death. In some gastric cell models, VacA-induced mitochondrial dysfunction, ER stress, and ATP depletion drive a mixed phenotype involving apoptosis, autophagic cell death [112], or programmed necrosis, but these processes still originate from mitochondrial injury within the intrinsic pathway [113] [114].

Another important virulence factor, CagA has the opposite role. It can lead to the activation of PI3K signaling pathways that dampens apoptosis and is required for *H. pylori*-induced cell migration [115]. PI3K-driven pro-survival signaling cooperates with MAPK pathways. In gastric cancer cells, inhibition of any of the three major MAPK branches—ERK (via MEK1/2), p38, or JNK—enhances apoptosis after H. pylori infection, indicating that MAPKs normally provide partial protection from cell death during infection [116]. Consistent with this, ERK1/2 and p38 activation is more pronounced in $cagA^+$ strains and that this activation protects against epithelial apoptosis at least in part by upregulating the anti-apoptotic protein Bcl-2 [117]. Beyond kinase pathways, CagA can directly interfere with apoptotic control by reducing the expression of tumor-suppressive E3 ubiquitin ligases such as SIVA1 and ULF in SNU1 gastric cancer cells, a mechanism proposed to support gastric tumor development [118]. As previously mentioned, CagA can also protect epithelial cells from VacA-induced mitochondrial apoptosis by preventing VacA trafficking to mitochondria [86]. Together, these findings support a model in which VacA drives early mitochondrial apoptosis and tissue damage, whereas CagA, via PI3K/MAPK signaling and direct effects on apoptotic regulators, limits excessive cell loss and promotes a chronic, pro-carcinogenic infection.

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Other virulence factors can also influence apoptosis, for example the gamma-glutamyl transpeptidase (GGT) inhibits apoptosis and induces proliferation of gastric epithelial cells through the induction of cyclooxygenase-2, epidermal growth factor-related peptides and interleukin-8 [119].

H. pylori can also activate the extrinsic, death-receptor–mediated apoptotic pathway, but this effect is tightly regulated and often counterbalanced, especially during chronic infection. In gastric epithelial cells, infection upregulates Fas and sensitizes cells to TNF-related apoptosis-inducing ligand (TRAIL) and TNF-α, promoting engagement of death receptors such as Fas, TRAIL-R1/R2, and TNFR1. This receptor ligation leads to assembly of the death-inducing signaling complex (DISC), recruitment of FADD and procaspase-8, promote caspase-8 activation, and cleavage of BID, which links the extrinsic pathway to mitochondrial permeabilization and intrinsic apoptosis [120] [121]. H. pylori can also suppress apoptosis by inducing factors like FRA-1 [122] and by differentially affecting acute versus chronic infection; acute exposure accelerates epithelial apoptosis, whereas prolonged infection reduces apoptosis rates, helping infected cells survive [123] [124] . Collectively, these data support the view that an imbalance between apoptosis and proliferation—induced by *H. pylori* virulence factors—contributes to gastric carcinogenesis, and that eradication of *H. pylori* can at least partially normalize these processes [125].

5. mtDNA Mutations

H. pylori infection promotes genomic instability in gastric epithelial cells, affecting both nuclear and mitochondrial DNA (mtDNA). While the mutagenic impact on nuclear DNA partly stems from suppressed expression and activity of key DNA repair pathways, *H. pylori* similarly impairs mtDNA integrity, leading to increased mutation frequency, reduced mtDNA copy number, and compromised respiratory function [126]. In gastric adenocarcinoma cell lines (e.g., AGS cells), *H. pylori* exposure triggers mtDNA mutations predominantly in the hypervariable D-loop region—a non-coding regulatory element critical for mtDNA replication and transcription—along with rare heteroplasmic point mutations in protein-coding genes like cytochrome b (Cytb). The primary driver of *H. pylori*-induced mtDNA mutations is oxidative stress from mtROS overproduction, fueled by virulence factors like VacA. This oxidative burden causes base lesions, single and double strand breaks, adducts formation and base mismatch and depletion of mtDNA content, as observed in both in vitro models and gastritis patient biopsies [90] [127].

Mitochondrial base excision repair (mtBER) is a primary mechanism for correcting oxidative mtDNA damage with its key enzyme called apurinic/apyrimidinic endonuclease 1 (APE-1). Y-box binding protein 1 (YB-1) is implicated in mismatch repair, while DNA polymerase gamma (POLG), and DNA polymerase beta (POLB) would fill DNA gaps [128]. DNA ligase 3 is also a key element of the BER pathway- both in the nucleus and in the mitochondria- and it interacts with tyrosyl-DNA phosphodiesterase 1 (TDP1), NEIL1/2 glycosylases and POLG [129]. During *H. pylori* infection, oxidative stress leads to accumulation of mtDNA lesions, which triggers activation of BER pathways. YB-1 has been identified as participating in mitochondrial DNA repair, cooperating with APE-1 to maintain mitochondrial genome integrity under infection-induced stress [130]. Experimental knockdown of mitochondrial APE-1 and YB-1, heightens *H. pylori*-induced mtDNA mutation loads. These findings confirm that APE-1 and YB-1 actively protect mtDNA during infection, with multiple repair pathways converging to mitigate oxidative damage. However, persistent infection overwhelms these repair systems, leading to mitochondrial dysfunction and increased susceptibility to carcinogenesis [130].

The mitochondrial protein import complex, translocase of outer membrane (TOM), plays a crucial role in importing nuclear-encoded proteins required for mtDNA maintenance [62]. During early stages of infection, VacA transiently enhances mitochondrial import machinery and key factors for mtDNA replication and transcription such as POLG and TFAM; at later stages, however, VacA's effect on these processes diminishes [128].

MtDNA damage can lead to leakage of mtDNA fragments into the cytoplasm via mitochondrial outer membrane permeabilization caused by mitochondrial dysfunction and oxidative stress. Once

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in the cytoplasm, mtDNA acts as a damage-associated molecular pattern (DAMP) and is sensed by the cyclic GMP-AMP synthase (cGAS), which produces cyclic GMP-AMP (cGAMP). cGAMP activates stimulator of interferon genes (STING), triggering a downstream signaling cascade that induces type I interferon production and proinflammatory cytokines, integral to antiviral and inflammatory responses. Persistent activation of this cGAS-STING pathway by mtDNA from damaged mitochondria sustains chronic inflammation, contributing to gastric pathology associated with *H. pylori* infection [131].

Mitochondria has another two options to maintain quality control and mtDNA integrity; either by mitochondrial fusion, which allows the compensation of damaged mtDNA with normal mtDNA (it can maintain mutation rate below 80%)[132], or enabling the removal of damaged mtDNA with mitophagy [133]. As previously mentioned, both options are highly affected during *H. pylori* infection, leading to mutagenesis.

Furthermore, previous studies have investigated the association between mtDNA copy number in peripheral blood and GC risk. Some studies showed that higher mtDNA copy number is a risk factor to develop GC [134] or associated with poor prognosis with reduced survival period [135]. However, a recent article with an extensive meta-analysis found no discernible causal relationship between peripheral blood mtDNA copy number and GC [136].

In conclusion, *H. pylori*-mediated oxidative stress induces mtDNA damage that disrupts mitochondrial function. During early infection it promotes the increase of mitochondrial translocases and some mtDNA repair factors, such as POLG. However, during later stages of the disease, the repair mechanisms are overwhelmed, and DNA mutations are accumulating. In the nucleus, well-known oncogenes are induced, while in the mitochondria, genetic instability activates innate immune responses through the cGAS-STING pathway, promoting chronic inflammation and carcinogenesis in the gastric mucosa.

6. Mitochondrial Bioenergetics During Helicobacter Pylori Infection

H. pylori infection induces profound alterations in mitochondrial bioenergetics, which contribute to the metabolic reprogramming underlying gastric pathogenesis and carcinogenesis. As previously mentioned, VacA toxin targets mitochondria and impairs their function by disrupting the mitochondrial membrane potential, decreasing ATP production, and inducing metabolic stress within infected gastric epithelial cells. This mitochondrial dysfunction caused by VacA leads to reduced oxidative phosphorylation efficiency and triggers compensatory metabolic shifts towards glycolysis, a hallmark of cancer metabolism known as the “Warburg effect” [137].

Despite initial mitochondrial damage, host cells activate adaptive mechanisms for mitochondrial restoration. Sensing cellular energy deficits via AMP-activated protein kinase (AMPK) leads to enhanced mitochondrial fission and turnover, which facilitates clearance of mitochondrial toxins and helps recover mitochondrial function and ATP levels in a time-dependent manner. Mitochondrial fission and autophagy work coordinately to maintain metabolic homeostasis even under continued VacA exposure [138].

Additionally, ATP-dependent Lon protease, a mitochondrial matrix protease crucial for degradation of damaged proteins and maintenance of mitochondrial proteostasis, is upregulated during *H. pylori* infection. Lon protease protects mitochondrial function by eliminating oxidatively damaged proteins, thereby preserving respiratory chain integrity and preventing excessive ROS production. However, persistent infection and prolonged stress overwhelm this protease system, resulting in progressive mitochondrial dysfunction and increased susceptibility to malignant transformation [139].

Collectively, these studies demonstrate that *H. pylori*-induced mitochondrial disruption leads to impaired oxidative phosphorylation and energy production, rerouting cellular metabolism towards glycolysis. At the same time, mitochondrial quality control mechanisms such as AMPK-mediated fission and Lon protease activation attempt to restore bioenergetic balance. Failure of these compensatory responses contributes to mitochondrial dysfunction, oxidative stress, and gastric

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carcinogenesis, highlighting mitochondrial bioenergetics as a critical axis in *H. pylori* pathobiology and a potential therapeutic target.

7. Helicobacter Pylori Induced Dysregulation of Immune cells

H. pylori exerts a variety of effects on different immune cell types through its virulence factors and metabolic products, modulating both innate and adaptive immunity to promote persistent infection.

The bacterium induces production of cytokines and chemokines from both gastric epithelial cells and from immune cells [140] [141] [142]. The multiple cytokines in the gastric mucosa (including TNF, IFN-γ, IL-1β, IL-6, IL-8, and IL-18) are predicted to have proinflammatory effects, whereas IL-10 and TGF-β are cytokines that may limit the inflammatory response. The impaired integrity and basal membrane damage thus create a microenvironment favorable for persistent infection, chronic inflammation, and carcinogenesis. It is partially caused by mtDNA mutations and impaired repair mechanisms, leading to genomic instability and prolonged mitochondrial dysfunction [128]. Specifically, *H. pylori* activates NF-κB and MAPKs pathways in gastric epithelial cells, leading to secretion of IL-8, IL-6, IL-1β, and TNF-α. Members of the innate immune system (monocytes/macrophages and dendritic cells) will produce high levels of IL-1β, IL-6, TNF-α, IL-10 and IL-12 upon *H. pylori* infection. Kranzer et al. showed that human dendritic cells exposed to *H. pylori* produce IL-6, IL-8, IL-10, IL-12 and TNFa and they undergo maturation, however, DC activation and maturation are independent of the cagPAI and VacA status of *H. pylori* [143]. (Figure 1.)

Dendritic cells (DCs) also have the capacity to induce effector T cells at the mucosal sites. Khamri et al. demonstrated that *H. pylori*-stimulated dendritic cells can promote IL-1β/IL-23-dependent IL-17 production by $CD4^+$ T cells[143]. D4+ T cells, also known as Th cells are divided into Th1, Th2, Th17, Th22, Th9, regulatory T cells (Tregs), and follicular helper T cells (Tfh). *H. pylori* exert a complex $CD4^+$ T-cell response involving Th1, Th17, and regulatory T cells (Treg), each defined by characteristic cytokines. *H. pylori* stimulate dendritic cells to produce IL—12 to promote the differentiation to the Th1 type. Th1 cells mainly produce interferon-γ (IFN-γ), IL-2, and and IL-12. IFN-γ can activate macrophages and strengthen their ability to phagocytose and kill *H. pylori*. Th17 cells differentiate from naïve CD4+ T cells in the presence of cytokines such as TGF-β, IL-6, IL-21 and IL-23. Th17 cells secrete IL-17, IL-21, IL-22 and IL-23, which recruit and activate neutrophils, induce epithelial antimicrobial peptides, chemokines, and matrix-metalloproteinases, and contribute to chronic inflammatory damage [144].To limit excessive immune response and permit bacterial persistence, *H. pylori* expands regulatory T cells in the gastric mucosa. TGF-β plays a key role in the differentiation of induced Tregs. These Treg cells typically produce high levels of IL-10 and TGF-β, which suppress Th1/Th17 effector functions, dampen local inflammation, and impair bacterial clearance[145] [146]. *H. pylori* in general inhibits T cell proliferation and activation, partly through the action of VacA which interferes with calcium signaling and mitochondrial function in T cells, leading to cell cycle arrest or apoptosis. Additionally, *H. pylori* skews T helper cell differentiation towards Th1 and Th17 and Treg, which are balancing the level of inflammation while fail an effective bacterial clearance [145] [147].

IFN-γ produced by Th1 or gastritic cell cannot only induce phagocytosis by the macrophages, but also to produce bactericidal substances such as nitric oxide and reactive oxygen species, enhancing inflammation [148]. One of the host's defense strategies against *H. pylori* involves macrophage production of nitric oxide (NO) via inducible nitric oxide synthase (iNOS). In vitro studies have demonstrated that macrophages co-cultured with *H. pylori* can restrict bacterial growth through NO-dependent mechanisms. However, this bactericidal activity is often insufficient because the availability of the iNOS substrate L-arginine is limited. *H. pylori* induces arginase activity in macrophages, which competes for and depletes L-arginine, thereby reducing NO synthesis and enabling bacterial survival [148] [149].

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In macrophages, SMOX activity reduces intracellular spermine levels, an inhibitor of inducible nitric oxide synthase (iNOS), thereby promoting iNOS protein expression and nitric oxide (NO) production that enhances antimicrobial defense against *H. pylori*. Conversely, inhibition or knockdown of SMOX worsens bacterial clearance by impairing NO-mediated killing [97]. However, elevated NO can contribute to the buildup of reactive nitrogen species (RNS). Together with—another byproduct of SMOX catalysed reaction—H_2O_2 can enhance inflammatory pathways, mitochondrial dysfunction and mtROS production. Furthermore, SMOX-generated 3-aminopropanaldehyde is converted into the highly reactive electrophile acrolein. In gastric epithelial cells of H.p infected mouse models, acrolein forms stable adducts with DNA and proteins, causing genotoxic stress, DNA strand breaks, and mutations. Pharmacological scavengers of acrolein, such as 2-hydroxybenzylamine (2-HOBA), mitigate DNA damage and suppress gastric carcinogenesis in experimental models, highlighting the therapeutic potential of targeting SMOX-acrolein axis[93].

Neutrophils belong to one of the earliest and most abundant immune cells recruited upon *H. pylori* infection to the gastric mucosa. It is navigated by several factors, including the neutrophil-activating protein NapA, urease, and chemokines (notably IL-8) [150]. These factors can mediate the release l-selectin (CD62L) expressed on the cellular surface, with a subsequent up-regulation of the β2-integrins CD11b and CD11c, which are essential for transendothelial migration of neutrophils to areas of inflammation [151].Once neutrophils are activated they will be the major source of reactive oxygen species (ROS), myeloperoxidase, and pro-inflammatory cytokines including IL-8, IL-1β, TNF-α, and IL-10, thereby amplifying local inflammation and recruiting additional leukocytes[152]. This persistent ROS release and sustained inflammation contributes to epithelial injury, DNA damage, and, over the long term, gastric carcinogenesis.

Chronic inflammation with elevated cytokine level drives persistent mtROS production triggering activation of the NLRP3 inflammasome complex. The activation mechanism involves mtROS facilitating the release of mitochondrial damage-associated molecular patterns (DAMPs), including oxidized mitochondrial DNA, which promote NLRP3 inflammasome assembly. This leads to caspase-1 activation, processing, and release of pro-inflammatory cytokines IL-1β and IL-18, amplifying gastric mucosal inflammation [54] [99]. MtROS also directly activates NLRP3 by thioredoxin-interacting protein (TXNIP) dissociation from thioredoxin, an event that triggers inflammasome assembly independent of potassium (K^+) efflux. However, *H. pylori* limits full caspase-1 activation, enabling bacterial persistence despite inflammasome priming [153] [154] . Early during infection (around 6 hours), *H. pylori* upregulates NLRP3 mRNA expression via activities of cag pathogenicity island (cagPAI) and VacA toxins, but by 24 hours, NLRP3 protein levels are suppressed through induction of microRNA miR-223-3p and anti-inflammatory cytokine IL-10. This regulation results in accumulation of pro-IL-1β but limits production of the mature cytokine IL-1β, modulating the inflammasome output and preventing excessive inflammatory damage. However, external stimulation by microbial or environmental activators readily induce NLRP3 inflammasome formation and secretion of high amounts of mature IL-1beta cytokines in humans [155]. This fine-tuned control allows mitochondrial stress to prime the inflammasome without triggering full activation and pyroptotic cell death, thereby maintaining a state of chronic gastritis conducive to bacterial persistence and sustained host inflammation [156].

H. pylori infection could facilitate the persistance of follicles on which continuous follicular helper T-cell activation could lead to uncontrolled follicular B-cell proliferation. Gastric mucosa B cells (which are antigen-presenting cells; APCs) internalize bacterial antigens (for example urease, flagellin, outer-membrane proteins), presenting them to T helper cells. Upon activation, antigen-specific T helper cells will express CD40L which interact with CD40 on the B cells and drives their entry into S phase; simultaneously, Th1 cytokines (IL-2, IFN-γ) and Th2 cytokines (IL-4, IL-5, IL-6, IL-10, IL-13) promote clonal expansion, antibody secretion, and isotype switching from IgM to IgG, ultimately leading to the differentiation into plasma cells and memory B cells [157]. B cells produce antibodies, predominantly IgA at the mucosal surface and IgG systemically, which can neutralize

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bacterial factors and promote clearance, although this humoral response alone rarely eradicates the infection.

Chronic stimulation by *H. pylori* also drives expansion of regulatory B cells (Bregs), typically IL-10–producing $CD24^{+}CD38^{+}$ subsets, which dampen Th1/Th17 responses and contribute to bacterial persistence by suppressing excessive inflammation. Over years, sustained B-cell activation within acquired gastric mucosa-associated lymphoid tissue creates a setting in which genetic lesions such as*BCR3–MALT1* and other translocations can arise, leading to monoclonal proliferation and gastric MALT lymphoma [25].

H. pylori also inhibit the STING and RIG-I signaling via downregulation of IRF3 activation, suppressing type I interferon responses [158]. This immune modulation reduces bacterial clearance while promoting a tolerogenic environment facilitating chronic infection.

In summary, *H. pylori* orchestrates a multifaceted disruption involving epithelial and immune cells, modulating acid secretion, promoting mitochondrial ROS generation, and sustaining low level of chronic inflammation. The immune-modulatory strategy that simultaneously activates inflammatory responses and impairs immune clearance, contributing to persistent infection and inflammation-associated gastric malignant transformation.

7. The role of Mitochondrial Stress in H. pylori-Linked Gastric Cancer

7.1. Different Haplotypes Polymorphism and Strains of H. pylori and Their Pathogenic Features

Although around 50% of people are infected with *H. pylori*, only a very small percentage will develop cancer. The likelihood of developing malignancies reflects an interaction between bacterial strain diversity, host genetic polymorphisms, and population background. Certain *H. pylori* haplogroups, such as the East Asian strains carry highly virulent constellations of virulence factors. On the host side, functional polymorphisms in the genes of pro- and anti-inflammatory cytokines (for example IL-1ß, TNFα, IL-10) and innate immune receptors such as TLR4 can modify the inflammatory response to the infection. Combinations of high-risk host genotypes and high-risk bacterial strains can amplify gastric cancer odds up to ten-fold relative to low-risk constellations.

A meta-analysis using data from BioBank Japan found that Germline pathogenic variants in nine genes (APC, ATM, BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, and PALB2) were associated with the risk of gastric cancer [159].

H. pylori has many strains, which exert very different virulence and malignant potential. CagA is widely recognized as the first identified bacterial oncoprotein, classified as a class 1 oncoprotein by the WHO, and CagA-positive strains elevate GC odds ratios 2-5-fold. The risk of GC is further increased when individuals are infected by strains expressing the CagA containing a high number of repeats its C'-terminal variable region or the D-type of this EPIYA motif [160]. VacA s1/m1 alleles synergize by exacerbating epithelial damage. Infection induces hypochlorhydria via parietal cell loss, promoting bacterial overgrowth and carcinogenic nitrite formation.

Additionally, CM motif polymorphisms—variations in sequence and copy number—differentiate Western-type and East Asian-type CagA. Western strains typically harbor two CM motifs with moderate SHP2-binding affinity, while East Asian CagA possesses a single but higher-affinity CM motif variant, correlating with increased virulence and gastric cancer risk in East Asian populations [84].

Overall, the CM motif-mediated oligomerization of CagA serves as a molecular amplifier, potentiating CagA-SHP2 interactions and oncogenic signaling cascades critical for *H. pylori* pathogenesis.

7.2. Gastric Cancer-Specific Mitochondrial Alterations Beyond Acute Infection

H. pylori-induced mitochondrial stress in GC manifests as a shift toward the Warburg effect, with upregulated glycolysis and suppressed oxidative phosphorylation (OXPHOS) supporting proliferation under hypoxia. Complex I deficiency from mitochondrial DNA (mtDNA) mutations

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reduces ATP production, downregulating peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) while upregulating glutaminase (GLS1)-driven glutaminolysis. Phosphorylated (Ser616) Drp1 hyperactivation coupled with Mfn1 and OPA1 suppression generates fragmented mitochondria that enhance invasion and metastasis [130]

Mitophagy is first induced in order to remove damaged mitochondria. CagA is helping this process, which favors pro-survival signaling without triggering apoptosis. However, later the damage will overwhelm the clearance, and damaged mitochondria will be accumulated. The impaired PTEN-induced kinase 1/Parkin (PINK1/Parkin)/microtubule-associated protein 1A/1B-light chain 3 (LC3-II) favors apoptosis resistance through Bcl-2 upregulation/Bax downregulation. Transcription factor A, mitochondrial (TFAM) downregulation and DNA polymerase gamma (POLG) upregulation fail to compensate for mtDNA loss, perpetuating genomic instability characteristic of GC progression. [130]

7.3. mtROS-Mediated Apoptosis Evasion and Tumorigenesis

H. pylori infection associated mtROS play a complex role in gastric cancer, contributing both to apoptotic cell death and to tumorigenesis by facilitating apoptosis evasion. Elevated mtROS levels can induce mitochondrial membrane depolarization, cytochrome c release, and activation of caspase-dependent apoptosis, serving as a tumor-suppressive mechanism to eliminate damaged cells. Several anticancer drugs exploit this by enhancing mtROS production to trigger apoptosis and cell cycle arrest in gastric cancer cell lines [161].

Conversely, chronic mtROS generation can promote gastric tumor progression by activating oncogenic signaling pathways such as β-catenin/Wnt, MAPK, and STAT3, and by inducing DNA mutations and genomic instability [158]. Tumor cells often develop mechanisms to evade mtROS-induced apoptosis, including upregulation of antioxidant defenses and alteration of mitochondrial dynamics, allowing them to tolerate oxidative stress and sustain proliferation.

Thus, mtROS create a dual effect in gastric cancer biology: low to moderate ROS levels act as signaling molecules promoting tumor growth and survival, while excessive ROS trigger apoptosis.

mtROS-induced mtDNA mutations [130], accumulate through the Correa cascade and correlate with Lauren histotypes: intestinal-type GC shows mtDNA stability, while diffuse-type exhibits hypermutation. The mtROS-NF-κB loop sustains STAT3/YAP/β-catenin signaling, promoting cadherin 1 (CDH1) loss—a diffuse GC hallmark—and peritoneal metastasis.

7.4. Mitochondria-Targeted Therapeutic Strategies for H. pylori-Associated GC

H. pylori eradication remains the cornerstone (30-50% GC risk reduction), though antibiotic resistance limits efficacy. Chemotherapy is the major treatment for gastric cancer especially in advanced cancer stages, however the combination of 2 or even 3 agents are preferable due to their synergism and lower side effects. For example, nanoparticle-delivered mitochondrial antioxidants overcome resistance, potentiating cisplatin efficacy. Clinical trials of using Drp1 inhibitors after *H. pylori* eradication also show potential therapeutic benefit [130] [162].

8. Mitochondrial Stress in Helicobacter pylori-Associated MALT Lymphoma

8.1. Helicobacter pylori Infection in MALT Lymphoma: Pathogenic Significance

The prevalence of *H. pylori* infection is very high in patients diagnosed with gastric MALT lymphoma, highlighting the role of *H. pylori* infection in its pathogenesis[163]. The unique ability of *H. pylori* to manipulate host immune responses, including the downregulation of T-cell cytotoxicity and the induction of tolerogenic dendritic cell phenotypes, supports the persistence of lymphoma.

Unlike gastric cancer (cagA$^+$ vacA s1/m1 dominant), MALT lymphoma associates with less virulent *H. pylori* strains, optimized for chronic immune evasion [164].

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The pathogenesis of MALT lymphoma involves a longer antigenic stimulation without the apoptosis of the host cells. The CagA negative are dominantly the responsible strains for the pathogenicity. The genotyping of the strain can predict eradication success; cagA negative, without t(11;18) translocation are the easiest to cure with rituximab treatment.

This longer immunological stimulation induces lymphoid follicles in the gastric mucosa, then evolve to the polyclonal lymphoid hyperplasia and further toward the generation of oligoclonal then monoclonal B cell population [6]. The reasons behind this progression, however, are not fully understood.

The progress of the disease can be linked directly and indirectly to *H. pylori* infection. The indirect route is through *H. pylori*- specific T-helper cells connecting to the B-cells via CD40L/CD40, triggering various downstream intracellular pathways. Besides, FOXP3+ regulatory T-cells release cytokines, chemokines, and costimulatory molecules that participate in the evolution and maintenance of the neoplastic B-cell population [165]. On the other hand, CagA can directly phosphorylate SHP-2, and activate the downstream signaling, either through ERK- p38MAPK, or via Bcl-XL/Bcl-2 to induce proliferation and to inhibit apoptosis.

At the molecular level, chronic stimulation favors the acquisition of characteristic chromosomal translocations such as t(11;18)(q21;q21) *BCR3–MALT1*, t(1;14)(p22;q32) *BCL10-IGH*, and t(14;18)(q32;q21) *IGH-MALT1*. *BCR3-MALT1* translocation (t(11;18)) in 20-30% confers *H. Pylori*-independent signaling through the canonical NF-κB pathway [166]. By contrast, the t(1;14)(p22;q32) translocation drives overexpression of BCL10, often with alterations in its CARD (caspase recruitment domain), which likewise leads to constitutive NF-κB activation. Collectively, these genetic lesions have established aberrant activation of the classical NF-κB pathway, which is a central mechanism in the pathogenesis of MALT lymphoma. (Figure 2.)

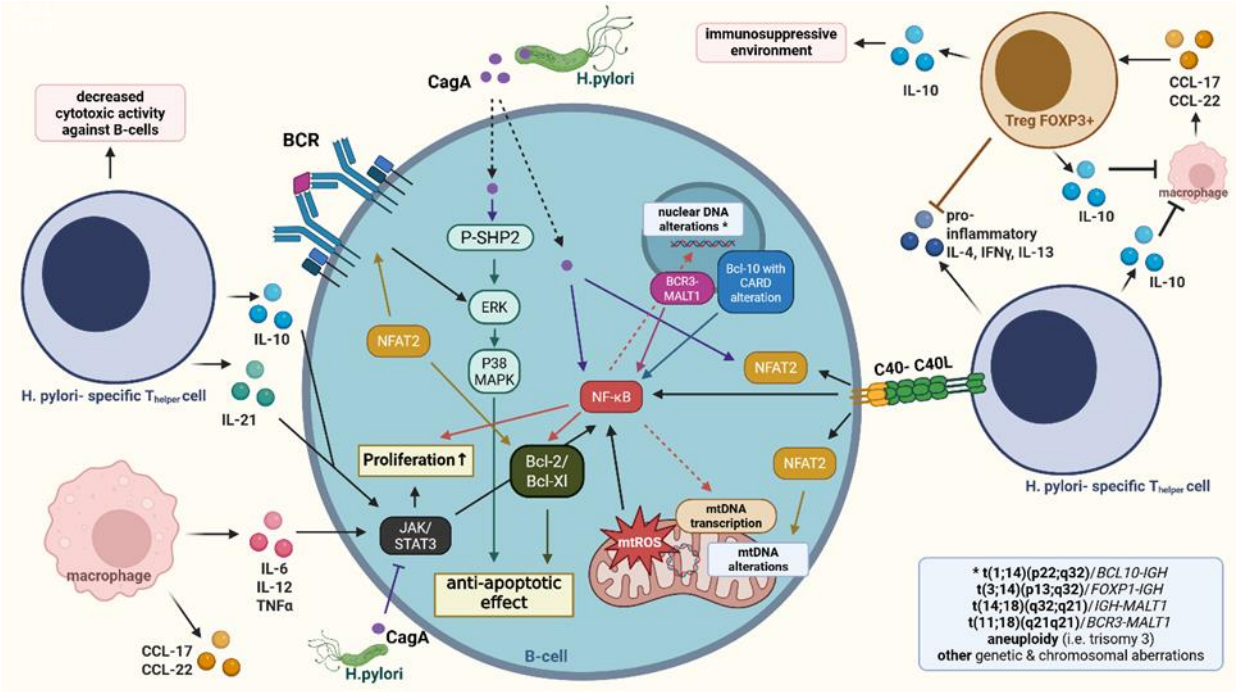

Figure 2. In gastric MALT lymphoma, chronic Helicobacter pylori–driven signaling integrates *H. pylori* virulence factors with B-cell receptor (BCR) and T-cell–dependent pathways to promote antigen-driven proliferation and cell survival, and later antigen-independent tumor cell proliferation. CagA, delivered by the bacterial type IV secretion system, can engage SH2-domain–containing host proteins, contributing to the activation of ERK and p38 MAPK. This reinforces a pro-survival, pro-proliferative environment that favors the expansion of antigen-stimulated B cells.

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Our knowledge of the role of mitochondria in MALT lymphoma development and progression is limited, with mitochondrial reactive oxygen species (mtROS) production, mtDNA alterations, and NF- κB effect on mtDNA transcription being the main involvement according to current literature. ,

NF-κB, a central molecule in MALT-lymphoma development and progression, can translocate to the mitochondria, binding to the mtDNA promoter regions to upregulate TFAM and CYTB, sustaining OXPHOS and mtROS–dependent survival signaling.

In parallel, persistent cytokine and receptor signaling converges on NF-κB, which becomes constitutively active once characteristic chromosomal translocations arise, such as *BCR3–MALT1* or *BCL10/IGH* rearrangements, locking in survival and growth signals even in the absence of ongoing antigen presence.

Within the lymphoma clone, chronic BCR engagement and CD40 ligation by *H. pylori*-specific T-helper cells are central drivers of altered intracellular signalling. BCR downstream signalling provides Ca^{2+} flux and mitochondrial ROS that leads to sustained NFAT2 activation, while NF-κB both cooperates with NFAT2 on target genes and can upregulate Nfatc1 itself.

This NFAT2–NF-κB–mitochondria axis helps in the maintenance of cell survival, ongoing proliferation, and resistance to apoptosis in the marginal-zone B-cell clone, creating a permissive background in which NF-κB–activating chromosomal translocations (such as *BCR3–MALT1/BCL10*) can induce antigen-independent cell proliferation and cell growth.

Furthermore, both NF- κB and NFAT2 upregulate the expression of anti-apoptotic molecules, such as Bcl-2/Bcl-Xl, further shifting the cell survival balance towards an anti-apoptotic state. In addition, the complex cytokine signals present in the *H.pylori*- infected gastric mucosa further promotes B-cell survival, proliferation, and apoptosis inhibition. These cytokines include the pro-inflammatory IL-4, IFNγ, IL-13, IL-6, IL-12, TNFα, CCL-17, and CCL22; and the anti-inflammatory IL-10 and TGFβ. The constellation of inflammatory cells and their cytokine expression pattern results in an immunosuppressive environment and decreased CD4+ cell cytotoxic effect in the *H.pylori*-infected gastric mucosa, fostering the development of MALT-lymphoma.

Over time, the combination of sustained NF-κB signaling and *H. pylori*–conditioned cytokine milieu facilitates the selection of B-cell clones harboring NF-κB–activating chromosomal translocations, completing the transition from reactive lymphoid hyperplasia to antigen-independent MALT lymphoma.

The most common genetic alterations are listed in the vignette in the right bottom part of the image.

Solid standard arrow: induction/activation; Solid blunt/T-bar arrow: blocking/inhibition; Dashed line: translocation.

Created in BioRender. Wappler-Guzzetta, EA. (2025) https://app.biorender.com/illustrations/6939ad8b8e22a2d07bb5d84e?slideId=8a60beb1-e4f2-42f8-a428-920db0d7648d (accessed on 12/12/2025)

8.2. Mitochondrial Stress in MALT Lymphoma

Emerging evidence positions NF-kB signaling as a key player in MALT lymphoma pathogenesis. In early, *H. pylori*–dependent MALT lymphoma, NF-κB activation is primarily extrinsically driven by chronic BCR and CD40 signaling, with modulation by CagA-induced ERK/p38 MAPK pathways and cooperation from NFAT2. This stage remains reversible with *H. pylori* eradication. However, the continuous antigen stimulation leads to chromosomal translocations, such as t(11;18)(q21;q21), t(1;14)(p22;q32), and t(14;18)(q32;q21). In this stage NF-κB becomes intrinsically and constitutively active, locking in B-cell survival and proliferation regardless of ongoing infection. NF-kB then exert many anti-apoptotic effects and promote proliferation; for example, upregulates genes such as Bcl-2, Bcl-Xl, and various inhibitors of apoptosis, and also induces cell-cycle regulators. The latter mechanism drives antigen-independent proliferation, explaining why these lymphomas often fail to regress after *H. pylori* eradication. In addition, NF-κB upregulates chemokines and cytokines that attract and polarize T cells and other immune cells, helping maintain the CD40L- and cytokine-rich

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niche that further stimulates BCR/CD40 and NF-κB itself. NF-κB activation can even enhance the expression of *BCR3–MALT1* fusion gene, creating a self-reinforcing loop. This NF-κB–centered signaling architecture is the core molecular engine that drives the transition from reactive lymphoid hyperplasia to overt, *H. pylori*–independent MALT lymphoma.

In the case of the gastric epithelial cells, VacA-induced mitochondrial depolarization and outer membrane permeabilization can trigger cytochrome c release and apoptosis. Therefore, we can hypothesize a similar mechanism in B cells, where chronic inflammation can lead to a persistent, sublethal level of mtROS production. We assume that mtROS can further enhance NF-kB activation via 3 mechanisms:1, mtROS generated at complexes I and III can oxidatively activate redox-sensitive kinases such as c-Src and MAP3Ks, which lie upstream of the IKK complex. Activated IKK phosphorylates IκBα, leading to its degradation and the release of NF-κB (typically p65/p50) to translocate into the nucleus and drive transcription of target genes.2, ROS promote tyrosine phosphorylation (rather than the classic serine phosphorylation and degradation) of IκBα, which can also permit NF-κB activation without complete IκBα proteolysis. This mechanism has been shown in hypoxia and TNF-α models.3, NF-κB induces expression of mitochondrial antioxidants like MnSOD (SOD2) and other redox regulators. This would create a feedback loop where mtROS activate NF-κB, and NF-κB then partially restrains mtROS to keep them at a “signaling” rather than a “toxic” level. [168]

It is important to mention that while low level mtROS typically enhance NF-κB activity and favor survival, inflammation, and pro-survival gene expression, high mtROS or oxidative burst would inhibit IKK or damage NF-κB components, or push the cell toward apoptosis instead of adaptive signaling. In case of B cells, the low-grade mtROS output from stressed mitochondria is entirely consistent with sustained NF-κB activation and survival signaling, even though the exact quantitative relationship in MALT has not been tested experimentally.

Evidence from biochemical fractionation and imaging shows that NF-κB subunits such as RelA and IκBα can be found in mitochondrial fractions and can bind mitochondrial DNA regulatory regions, where they modulate transcription of some mitochondrial genes (for example COX subunits and Cyt b)[167]. Import of IκBα into mitochondria is stimulus-dependent (e.g., TNFα, hypoxia) and may involve components of the outer-membrane import machinery such as TOM40 [146]. During early hypoxia, studies showed that a RelA/IκBα complex transiently accumulates in mitochondria and it was dependent on STAT3 phosphorylation. Cooperation between STAT3 and the RelA/IκBα complex has been described to preserve mitochondrial function and cell viability[169] [170].

Mitochondrial RelA/IκBα has been implicated in fine-tuning OXPHOS, mtROS production, and apoptosis sensitivity by adjusting expression of selected mtDNA-encoded respiratory chain components. Therefore mitochondrial NF-κB signaling helps tumor cells to survive by downregulating apoptosis and regulating mitochondrial stress. (Figure 2)

9. Conclusions

As above detailed, *H. pylori* infection, besides its common and widely known pathological and microbiological effects, is responsible for numerous mitochondrial stress-driven GC and MALT lymphoma tumorigenesis and cancer progression. Our knowledge in this field is, however, currently limited. Future pre-clinical and clinical studies investigating the role of *H. pylori*- associated effects on mitochondrial stress, metabolism and dynamics can lead to additional therapeutic options in these malignancies.

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Abbreviations

Abbreviations are detailed in the text at their first appearance.

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