Helicobacter pylori and Immune Evasion in Gastric Carcinogenesis

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Declaration

It is hereby declared that

- The thesis submitted is our original work while completing the degree at Brac University.
- The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
- The thesis does not contain material that has been accepted, or submitted, for any other degree or diploma at a university or other institution.
- We have acknowledged all main sources of help.

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Abstract

Helicobacter pylori is found in approximately half of the global population, often without causing any symptoms of disease. Its infection is a significant public health concern and has been extensively researched for its role in gastric carcinogenesis, primarily due to its ability to evade the body's immune system. This review will examine the complex relationship between *H. pylori* and the host's immune response, emphasizing how immune evasion contributes to the prolonged infection that precedes cancer. By evading the immune system, this bacteria establishes a persistent infection and creates an environment favorable to cancer development. In conclusion, this article seeks to provide an overview of current knowledge and recent discoveries regarding *H. pylori's* immune evasion strategies and their impact on the progression of gastric cancer. The information presented could aid in more effective methods for managing and preventing *H. pylori*-related gastric cancer.

Keywords: *Helicobacter pylori*, gastric carcinogenesis, immune evasion, virulence factors, chronic gastritis, CagA, VacA, Urease, Gastric cancer, inflammation

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Chapter 1

Introduction

1.1 Gastric Carcinogenesis Overview

Although its prevalence has declined recently, gastric cancer (GC) is still one of the world's top causes of cancer-related mortality. For instance, in total, 1.1 million new cases and 770,000 deaths of gastric cancer were estimated in 2020. Gastric carcinogenesis is a multistep, complex process involving the transformation of normal gastric epithelial cells into cancerous cells because of the accumulation of molecular and cellular changes. This multistep process is initiated by various events, which may include environmental influences, intrinsic and extrinsic influences, and the presence of risk factors. Chronic active gastritis can also lead to unfavorable long-term outcomes, including atrophy and metaplasia. The mucosal atrophy then degenerates into a condition known as dysplasia, which is the main precursor to the development of invasive malignancy. Based on this process of gastric carcinogenesis, researchers have identified different subjects of concern and a variety of molecular targets that might provide a strategy for the prevention and management of gastric cancer patients. Immune system function, oxidative stress, apoptosis, and necrosis are among them. In general, effective treatment or management can be achieved when gastric carcinogenesis is well understood or predictable based on its precursors and molecular pathogenesis.

The development of gastric cancer from normal gastric mucosa can be described and divided into several steps, such as chronic gastritis, which may lead to atrophic gastritis, metaplastic gastritis, dysplasia, and the final state of gastric cancer. The interactions between various intrinsic and extrinsic risk factors determine the alleles, rather than any specific point mutation, and all of these factors have an additive influence on cancer development. Host bacterium interactions were emphasized, as were possible primary cancer prevention methods and oncological mechanism developments. All of these developments ultimately lead to the transfer of these basic mechanisms to the clinical setting for the treatment of gastric cancer patients. Similar to numerous other forms of cancer, gastric cancer (GC) develops as a result of a complex interplay between hereditary and environmental factors. Over the past few decades, it has become more widely acknowledged that microorganisms have a role in the development of stomach cancer among environmental factors. Historically, the human stomach was thought to be virtually sterile due to the harsh conditions of the gastric ecological niche until the discovery of *H. pylori* in the 1980s. The primary risk factor for gastric cancer (GC) and other gastroduodenal disorders is

generally agreed to be *H. pylori* infection, and its pathogenic mechanisms have been thoroughly studied. On the other hand, not much is known about the role that other stomach microbes play in the development of gastric cancer. However, in recent years, there has been a lot of focus on the stomach's overall microbial population and how it contributes to GC and nontumorous gastric illnesses.

Helicobacter pylori is a gram-negative bacterium that generally resides in human gastric mucosa. *H. pylori* is present in about 90% of the population in developing countries and up to 50% in industrialized Western countries. It causes chronic infection in the stomach, which can lead to the development of atrophic gastritis and eventually gastric and duodenal ulcers and neoplasia, such as adenocarcinoma of the stomach and the mucosa-associated lymphoid tissue lymphoma (Miller & Williams, 2021). The mode of transmission of *H. pylori* is generally person-to-person via fecal-oral or oral-oral routes. In populations with a high prevalence of infection, such as in Africa, *H. pylori* infection is primarily acquired at a young age, typically during childhood.

H. pylori can colonize the human stomach because it has adapted to survive in the harsh acidic environment of the host gastric mucosa. *H. pylori* induces chronic active gastritis by infiltrating the gastric mucosa and inducing potent inflammatory responses leading to the activation of pro-inflammatory cytokines such as interleukin-1, IL-6, and IL-8. Although colonization with *H. pylori* often induces mild gastritis, which may be asymptomatic, this increasingly emerges as a treatable cause of some gastrointestinal pathology. The syndrome of duodenal ulcer disease is the final common pathophysiological result of a complex series of interactions between *H. pylori* and mucosal inflammatory responses. In the gastrointestinal system, the first focus is on acid secretion and defense in a healthy state, then we explore *H. pylori* as a common cause of several duodenal disorders (Gupta et al.2023). The stomach offers *H. pylori* a unique life niche once it gains the capacity to live. Host inflammatory/immune cells can't pass from blood vessels through the stomach epithelial mucosa to identify and combat invasive microorganisms. Rather, the inefficient host cells keep reacting to the infection site, where they perish and discharge nutrients that provide the stomach pathogen with food.

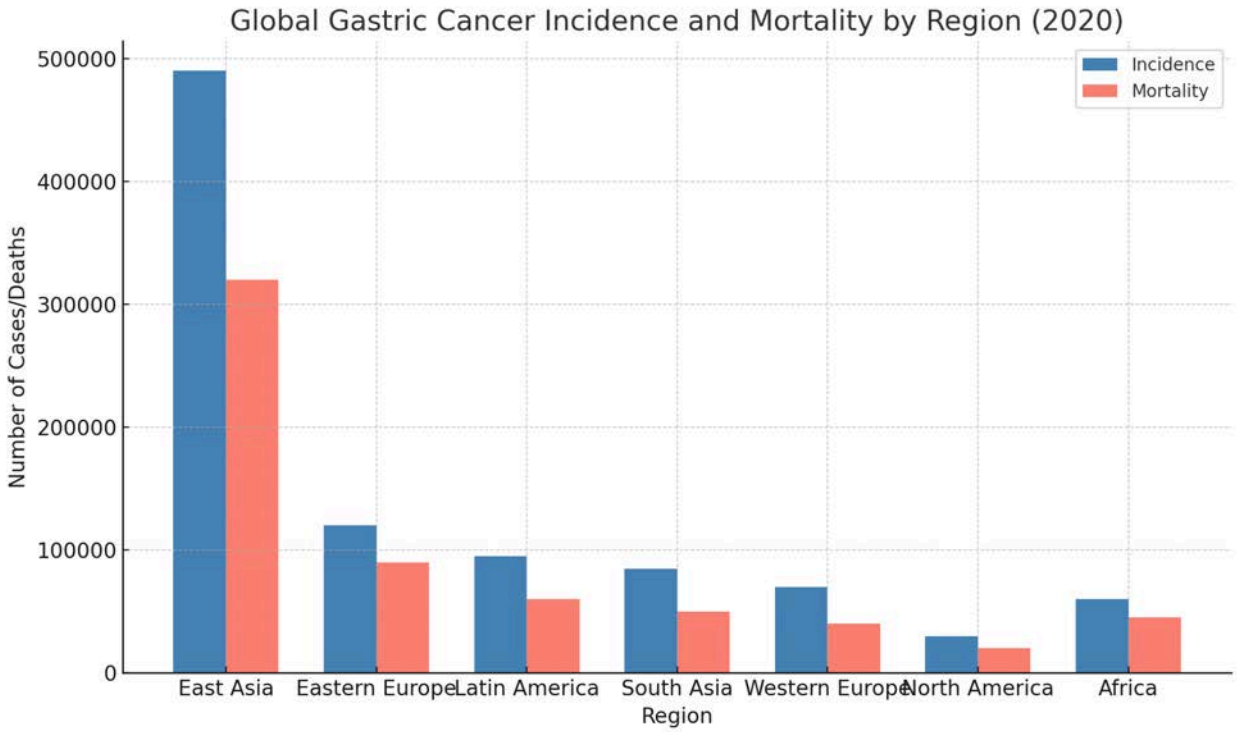

Fig. 1 Global incidence and mortality of gastric cancer by region in 2020

1.2 Discovery of *Helicobacter Pylori*

In 1982, Barry Marshall and Robin Warren surprised the scientific community by announcing that they had isolated a spiral-shaped bacterium from the stomach. No less controversial was their proposal that this bacterium was associated with duodenal and gastric ulcers, conditions that many physicians had believed for more than a century were caused by too much stress, alcohol use, smoking, or spicy foods (Lee, 2021). Even with a newly isolated bacterial agent, few believed that an infection was the cause of ulcers, and Marshall had to resort to infecting himself to convince mainstream medicine of the role of *H. pylori* in peptic ulcers. The dogma of a stress-related, psychosomatic origin of ulcers is an example of a long-standing belief in the face of compelling evidence to the contrary, and *H. pylori* is an example of how the microbial causes of diseases are often overlooked (Jin et al., 2024).

What became known as *H. pylori* was isolated in 1982 by Robin Warren from a patient with gastritis, from a diseased mucosa biopsy for the examination of biopsies submitted to the pathology laboratory. Warren had worked for many years as a pathologist and had noticed the spiral-shaped bacteria on the histological slides that he had prepared and stained. The biopsy was streaked onto the first culture plate of mucin blood agar, proliferated, and then fulfilled one of the "postulates": the pathogenic microorganism must be isolated in a pure culture away from diseased tissues (Maity & Naagar).

H. pylori with a characteristic spiral or 'S' shape can display motility. *H. pylori* is unique in its ability to produce large quantities of urease, and this plays a critical role in the survival and multiplication of the organism in the human stomach. Urease is a cytosolic protein that catalyzes the hydrolysis of urea to carbon dioxide and ammonia. This ammonia neutralizes acid around the bacteria and also gives the bacterium local alkalinity, because the concentration of carbon dioxide is very low in the gastric fluid. The combined action of several urease enzymes is considered necessary to produce sufficient ammonia to protect *H. pylori* from the potent acid of the stomach (Uberti et al.2022). *H. pylori* has a low percentage of 'conserved' genes in its genome, largely due to multiple restriction/modification systems that result in high rates of mutation and recombination, and a correspondingly high rate of genome 'plasticity'. There is a high level of genetic diversity seen in *H. pylori*, and this likely has implications for the

pathogenesis of the organism. Although *H. pylori* is able to utilize many substrates as a carbon and energy source and has a great capacity to tolerate stress conditions such as heat, pH, osmotic shock, and oxidative stress, some characteristics of the organism limit its colonization of some environments, and these include oxygen sensitivity and relatively few possible energy-generating metabolic pathways, unlike *Escherichia coli*, which has four possible energy-generating pathways. *H. pylori* is considered to be the most common chronic bacterial infection found in the gastric mucosa, and about 30% of the population is colonized with this bacterium. In areas of the world with poor sanitation, the rate of colonization is high, upwards of 60%. The bacterium is found more often in individuals of low socioeconomic status and congested living conditions. The transmission route is believed to be fecal to oral, oral to oral, and possibly oral to gastric. *H. pylori* is associated with several gastroduodenal diseases including chronic active gastritis, peptic ulcer disease, primary gastric lymphoma, gastric adenocarcinoma, and carcinoid tumors (Schulz & Kupčinskas, 2020).

1.3 Epidemiology of *Helicobacter Pylori* bacteria

*H. pylori i*s one of the most common human pathogens, and over 4.4 billion people worldwide are estimated to be *H. pylori* carriers. There is wide variation in prevalence observed between *H. pylori* infections in different countries, ranging from 20% to 80%. Developing countries have statistically significantly higher prevalence rates (80–90%) in at-risk populations when compared with developed countries (20–30%). (Reshetnyak et al.2021)

H. pylori is predominantly transmitted by the fecal-oral or oral-oral route. Infection by *H. pylori* occurs vertically from mother to child and is influenced by multiple risk factors, such as poverty, lower socioeconomic status in the community, crowding in households with poor hygiene, and low levels of education in the population. The socioeconomic determinants, such as overcrowding, sharing a bedroom and bathroom, and limited water and food resources, pose a greater risk to family members. Age, gender, and geographic location are the major determinants of *H. pylori* infection distribution in the population (Kim, 2024).

Socioeconomic status, family size, household income, poor housing, water supply, and household crowding were considered the main risk factors for *H. pylori* seropositivity in Korea and in developing countries, where poor household crowding, several family members per night in one room, or sharing a house with a leaking roof were associated with an increase in children infected with *H. pylori*. In relation to the transmission risk factors in low-income countries, crowded households were significantly correlated with a four-fold increase of *H. pylori* in coastal South India. As a result, the vertical infection prevalence is higher among poor individuals, those affected by psychiatric diseases, and HIV-positive pregnant women (Almadi et al., 2024). The geographical area was also identified as an infection determinant among carriers and health programs, where *H. pylori* infection rates were significantly different between the inhabitants of the central and southern regions, compared to the lack of geographical factors such as rural and urban residence.

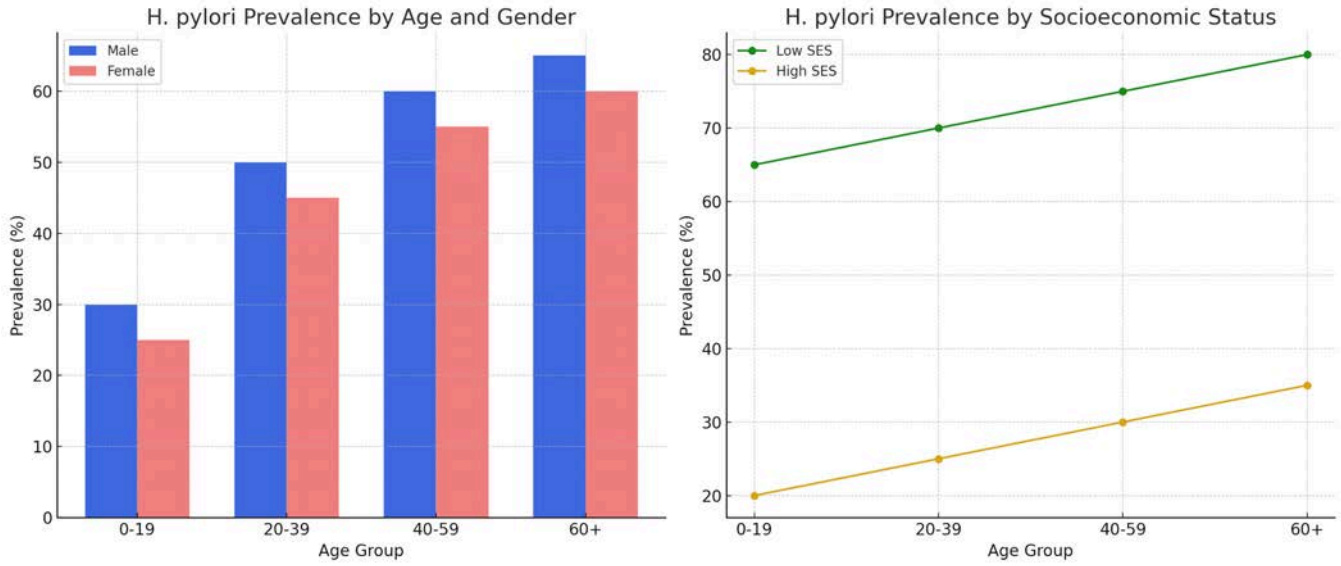

Fig. 2 Prevalence of Helicobacter pylori infection based on age and gender(left), and socioeconomic status(right).

1.4 Demographic patterns of H. pylori

To comprehensively understand the transmission and impact of *H. pylori* in a population, it is important to be resolute in understanding the proportions affected across subpopulations defined by various demographic measures including sex, age, ethnicity, country of birth, residential location, and lifestyle.

There is agreement that the infection with *H. pylori* is usually acquired at a young age ante-or intra-natally, although the rates of delayed acquisition exist in special cultural populations, including those populations already industrialized. For the most part, the age at which acquisition occurs requires empirical data to ascertain, though retrospective collection is prone to bias. Cohort studies devoid of selection, recall, and survival bias are necessary for the evaluation of an association with the disease. Cross-sectional studies of people who have little overseas travel have been done to estimate infection risk. In particular, the ratio of infected people in a population between infants or children and adults or elders has been used to estimate the duration of transmission in different populations (Araújo et al., 2022).

Socioeconomic status: There are no consistent patterns to suggest that rates of *H. pylori* infection vary by socioeconomic status. Data suggest that poverty is not associated with infection in many urban settings. In a cohort of Black inner-city and White suburban children, there was no difference in infection rates by race or socioeconomic status. However, lower socioeconomic status was associated with increased infection for White children. In Latin American countries, *H. pylori* infection rates decrease with increasing per capita income. A study determined that *H. pylori* rates in Queensland are indistinguishable by socioeconomic status in grades one and ten. Another study determined that rates of infection among students 12 to 19 years of age are indistinguishable by socioeconomic status. Such data suggest that the potential of environmental-modifiable risk factors varies by culture (Brown et al.2022). The appeal to highlight this body of data is the absence of potential subject bias. Since parental socioeconomic status is responsible for the differential infection rates seen in pediatric epidemiologic studies, one should always check infection rates by socioeconomic status. The lack of rise in infection with increasing socioeconomic status will provide a useful benchmark in appropriate rural and urban settings.

1.5 Risk factors and Mechanisms

The most well-established major risk factor for gastric carcinoma is infection, while the key triggers of multistep gastric carcinogenesis include genetic susceptibility, diet, poor socioeconomic conditions, high salt and nitrate consumption, reduced antioxidant intake, smoking, obesity, and pickling or smoking food. All of these factors can initiate a proximal cascade in the stomach. Patients who develop sporadic carcinoma generally experience inflammation, atrophy, intestinal metaplasia, and dysplasia sequentially before developing carcinoma. Socioeconomic status, medical care access, and public health infrastructure play an essential role in the high detection of gastric carcinoma in parts of the United States, Europe, and Japan. In some regions, certain populations have the highest incidence of gastric carcinoma. Although genetic susceptibility appears to be the primary cause of this increased incidence, it is crucial to recognize other environmental factors that may contribute to the development of this disease. In areas with a high prevalence of infection or areas with a high incidence of gastric carcinoma, proper public health prevention measures, such as eradication of infection or other measures, can reduce the incidence of this tumor, even if they are proven. The results must be confirmed at the population level by experts.

Chapter 2

Virulence Factors of *Helicobacter pylori*

As previously stated, *Helicobacter pylori* infects half the world's population, but the majority of infected individuals remain asymptomatic for the rest of their lives. However, a significant percentage of these individuals develop serious digestive pathologies such as peptic and duodenal ulcers, non-Hodgkin's lymphoma of the mucosa-associated lymphoid tissue, and even gastric adenocarcinoma (Kumar et al., 2020). The basis of this process is the malignant transformation of the gastric mucosa in response to the effects of chronically applied pathogenic factors belonging to direct inducers of the excessive immune response or impaired healing of the organ concerned by direct contact with *H. pylori* parenchyma and toxic secretion of colonies (Yang et al., 2021). Not all strains of these bacteria are inextricably linked to the above, as given strains possess factors without which they are not adequate in terms of oncogenicity.

One of the most important ways to adapt to the adverse environmental conditions of the human stomach is the constituents of the outer membrane, flagella, antigen, and more than 1500 different types of proteins located on the surface of progeny's pili. In addition, many factors secreted by the bacterium significantly contribute to the overall pathogenic potential, injury of the cells of the mucosa, defense mechanisms related to immunity, and the end organ. These multiple elements contribute to mitigating the risks associated with the severe apoptotic, immunological, and defensive environments established in response to challenges faced by the gastrointestinal tract. More than 1500 of this kind, including genetic endotoxin, urease, protease, and various adhesins, have been confirmed as pathogenic island enzymes associated with coding, transcription, flagella, urease, and adhesion (Sharndama & Mba, 2022). These proteins are important in the biogenesis of the human carcinogenic system.

Table 1. Features of *H. pylori* virulence factors that enable the development of cancer.

Virulence Factor	Description	Mechanism in Gastric Carcinogenesis
Cytotoxin-Associated Gene (CagA)	A protein is introduced into the cells of the host through the Type IV secretion system. CagA-positive strains are more virulent.	It interferes with the signaling pathways of host cells, leading to inflammation, cell proliferation, and the disturbance of cell polarity. This ultimately results in oncogenic transformation.
Vacuolating cytotoxin A (VacA)	Toxin triggers the creation of vacuoles in the host cells and leads to the programmed cell death of immune cells.	Contributes to immune evasion by eliminating T-cells, which results in prolonged inflammation and makes the gastric epithelium more susceptible to damage, increasing the risk of cancer.
Urease	The enzyme that facilitates the breakdown of urea into ammonia and CO_2, enables *H. pylori* to thrive in acidic environments.	Changes the acidity of the stomach environment by neutralizing acid, resulting in damage to the stomach lining, prolonged inflammation, and advancement toward the development of gastric cancer.

Lipopolysaccharide (LPS)	Component of the bacterial outer layer, identified by the immune system of the host.	It triggers an immune response and causes chronic inflammation. Its ability to mimic the structure of other molecules may also allow it to avoid detection by the immune system, thereby supporting ongoing infection.
Outer Membrane Proteins (OMPs)	Proteins that enable bacterial attachment to the cells lining the stomach.	Promotes bacterial colonization, which leads to persistent infection and ongoing inflammation, thus establishing an environment favorable for the development of cancer.

2.1 Cytotoxin-Associated Gene A (CagA)

The *H. pylori* bacterium has a high capacity for adapting to the human stomach environment. Infection with this is now recognized as the most significant risk factor for the development of gastric cancer. Mechanistic research has concentrated on unraveling the role that its virulence factors play in the emergence of this condition. CagA is a highly significant and pathognomonic *H. pylori* virulence factor. It is a protein that is produced by the cytotoxin-associated gene (cag) pathogenicity island, which is a specific segment of DNA located in particular virulent strains of *H. pylori* (Baj et al., 2020). The presence of CagA in these strains correlates with a heightened risk of serious gastric illnesses, notably gastric cancer. For decades, research on CagA has focused on elucidating its molecular actions and pathogenic mechanisms.

Epidemiological studies indicate that CagA determination in serum or gastric mucosa will become a helpful tool in evaluating gastric cancer risk (Yang et al., 2020). Inhibiting or impeding CagA-bearing *H. pylori* might serve as a therapeutic marker to prevent *H. pylori*-related diseases.

Thus, comprehending the profound interactions of host cells induced by CagA has led to intense research focusing on the molecular pathogenesis of *Helicobacter pylori*-associated gastric carcinogenesis.

Mechanism of Action:

The delivery of CagA into host gastric epithelial cells occurs through a specialized structure known as the Type IV secretion system (T4SS). Once inside the cell, CagA experiences a process of phosphorylation at specific tyrosine residues located within its EPIYA motifs, facilitated by host kinases (Wang et al., 2023). This phosphorylation enables CagA to engage with a diverse array of host signaling proteins, significantly interrupting regular cellular functions.

1. Activation of SHP-2 Phosphatase: The activated CagA protein stimulates SHP-2, a crucial tyrosine phosphatase that plays an essential role in cell signaling regulation. This improper activation of SHP-2 results in an overactivation of the Ras-Raf-MAPK signaling pathway, which in turn fosters excessive cell proliferation—a key characteristic often associated with cancer progression (Foster, 2023).

2. Disruption of Cell Polarity and Adhesion: CagA can bind with proteins located at epithelial junctions, such as ZO-1 and E-cadherin (Kuo et al., 2021). This interaction leads to the disruption of tight junctions and the overall polarity of the cells. The resulting impairment of cell adhesion and orientation promotes a phenomenon known as epithelial-to-mesenchymal transition (EMT), wherein epithelial cells acquire enhanced migratory and invasive characteristics, thereby aiding the spread of gastric cancer.

3. Chronic Inflammation via NF-κB Activation: In addition, CagA instigates the activation of nuclear factor-κB (NF-κB), a transcription factor instrumental in driving the synthesis of pro-inflammatory cytokines. The persistent activation of NF-κB results in chronic inflammation within the gastric environment, which serves as a significant catalyst for DNA damage and the eventual malignant transformation of gastric epithelial cells. (Yang et al., 2021)

Role in Carcinogenesis:

CagA-expressing strains of *H. pylori* play a pivotal role in the development of gastric adenocarcinoma, presenting a notably heightened risk factor. The presence of CagA triggers a disturbance in essential signaling pathways, which in turn leads to unchecked cellular growth and alteration of the normal tissue structure. This dysregulation fosters a state of chronic inflammation, all of which are key elements that drive the intricate multistep process of gastric carcinogenesis.

2.2 Vacuolating Cytotoxin A (VacA)

VacA is an important vacuolating cytotoxic protein secreted by *H. pylori*, which is responsible for many pathophysiological effects including cell vacuolation, cellular injury, degradation of the epithelial barrier integrity, and apoptotic signaling both in vivo and in vitro. In contrast to CagA, which penetrates and is introduced into host cells, VacA is released into the extracellular environment, where it influences a variety of cells, encompassing both epithelial and immune cells. VacA moves to the plasma membrane surface of susceptible cells, binds to them, and is taken up by endocytosis into the cells, acting on mitochondria and mitochondria-associated voltage-dependent anion channels (VDACs), resulting in cell vacuolation and ultimately apoptosis. (Luo et al., 2021)

In general, VacA impairs epithelial barrier integrity. It has a variety of effects on different cells because it can bind to a multitude of surface receptors on the surface of host cells. Immune-modulating activities of *H. pylori* have also demonstrated the impact of VacA on immunological functions. It has been suggested that this protein is associated with persistent colonization. The level of vacA transcription can be modulated rapidly according to the environmental changes of the host and some degree of immunity by the pH-regulated status, which is essential for successful and long-term infection (Capparelli & Iannelli, 2022).

H. pylori strains that contain both CagA and VacA are reportedly several times more probable to induce gastric lesions, whereas the chances of acquiring severe dyspeptic (pre-neoplastic) lesions are rarely positively correlated with the expression of solely VacA (El et al., 2020). Concerning *H. pylori* immunopathogenesis, it is critical to understand the methods that this bacterium exploits to settle in the stomach and also counteract the host defense mechanism which is discussed below.

Mechanism of Action:

1. Induction of Vacuole Formation: The protein VacA attaches to receptors located on the surface of gastric epithelial cells, initiating the formation of pores within the plasma membrane. This action disrupts the delicate balance of ions within the cell, resulting in the creation of large vacuoles that interfere with standard cellular operations (Sukhan et al., 2020).

2. Immune Evasion and Modulation: VacA hinders the functioning of immune cells, with a significant impact on T cells. It triggers programmed cell death, or apoptosis, in activated T cells and prevents their growth, which diminishes the immune system's ability to monitor and eliminate *H. pylori* (Lin et al., 2024). Consequently, this dysfunction allows for ongoing infection and contributes to chronic inflammation.

3. Mitochondrial Dysfunction and Apoptosis: VacA exhibits a predilection for host cell mitochondria, inflicting damage that prompts the release of cytochrome c, thereby activating the apoptotic pathway (Qureshi, 2021). This action not only affects the integrity of the gastric epithelial cells but also undermines the immune response by inducing the apoptosis of immune cells.

4. Modulation of Lysosomal Function: VacA disrupts the activity of lysosomes, which impedes the breakdown of damaged cells, thus favoring the survival of cells that may become malignant.

Role in Carcinogenesis:

VacA fulfills a dual role in fostering the development of gastric cancer by causing injury to epithelial cells and suppressing immune function. This, in turn, creates a pro-inflammatory environment that can accelerate the transition from chronic gastritis to gastric cancer. The ongoing inflammation and cellular damage instigated by VacA significantly enhance the likelihood of genomic instability, thereby promoting the process of malignant transformation (Lin et al., 2024).

2.3 Urease

H. pylori is unique among the entire set of bacteria. This microorganism produces urease, a constitutive enzyme without any requirement for induction. Produced in large amounts, it acts as the primary virulence factor of *H. pylori*, which can be antigenically different and important for the diagnosis of infection. Urease is a vital factor of *H. pylori*, which helps in its survival in an acidic environment. Urease is capable of transforming urea into ammonia and carbon dioxide. As urea diffuses much more abruptly from acid, ammonia produced as a result of the urease reaction increases the pH and helps more pathogens to survive (Motasim et al., 2024). The excretion of ammonia created by partially treated urease causes direct damage to the cells of the gastric epithelium and is one of the most important factors in causing gastric inflammation. In the oxidative environment of the gastric lumen, *H. pylori* bears its own risk. It bypasses this acid barrier by producing urease, which neutralizes the gastric acid. Additionally, excreted end-products of the enzyme get mixed in the gastric mucosa; basic pH is achieved due to the neutralization of the gastric acid.

Mechanism of Action:

1. Neutralization of Gastric Acid: Urease functions by producing ammonia, which acts to buffer gastric acid, consequently enabling *H. pylori* to establish itself within the stomach lining. This alteration results in a more favorable environment for the bacteria, facilitating the establishment of chronic infection.

2. Ammonia Production and Cellular Damage: The generated ammonia displays cytotoxic properties towards gastric epithelial cells, triggering oxidative stress and contributing to cellular injury. This ongoing damage is associated with a heightened risk of cancer development.

3. Immune Evasion: Urease plays a significant role in immune evasion by serving to neutralize stomach acid, which hinders the effectiveness of immune cells such as macrophages and neutrophils (Fan et al., 2024). This mechanism supports the sustained presence of *H. pylori*, leading to a persistent cycle of tissue damage and repair that fosters carcinogenesis.

Role in Carcinogenesis:

Urease is implicated in promoting gastric inflammation, cellular damage, and immune suppression—key elements that contribute to the onset of gastric cancer. Furthermore, its role in elevating oxidative stress and generating reactive nitrogen species (RNS) is associated with DNA damage in gastric epithelial cells, thereby increasing the probability of mutations that may lead to cancer.

2.4 LPS (Lipopolysaccharide)

Mechanism of Action:

1. Reduced Immunogenicity: The LPS of *H. pylori* does not bind as strongly to Toll-like receptor 4 (TLR4), an important receptor for identifying bacterial threats (Cheok et al., 2022). This change decreases the immune system's ability to recognize the bacterium and triggers a strong inflammatory reaction. By avoiding early detection by the immune system, this bacteria is able to establish a persistent infection in the stomach lining, leading to long-term inflammation, which is a crucial factor in the development of stomach cancer.

2. Chronic Inflammation and DNA Damage: Even though *H. pylori's* LPS elicits a less robust immune reaction, it still plays a role in persistent, mild inflammation. This sustained inflammation results in the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which induce DNA harm in stomach lining cells (Jain et al., 2021). The buildup of DNA damage gradually raises the likelihood of mutations, fostering the onset of gastric cancer.

3. Disruption of the Gastric Mucosal Barrier: LPS also plays a role in disrupting the gastric epithelial barrier, which leads to increased permeability of the gastric mucosa. This in turn allows bacterial products and toxins to penetrate further into the tissue, which amplifies inflammatory responses and contributes to additional damage to epithelial cells and the development of cancer.

Role in Gastric Carcinogenesis:

The prolonged presence of LPS leads to chronic inflammation, which plays a crucial role in the development of gastric cancer. Over time, persistent infection and inflammation cause cellular damage, genetic mutations, and the eventual conversion of gastric epithelial cells into cancerous cells. The prolonged ability of *H. pylori* to avoid the immune response allows it to persist in the gastric environment for many years, perpetuating the cycle of damage and repair that characterizes the progression from chronic gastritis to gastric cancer.

2.5 Outer Membrane Proteins (OMPs)

A) Blood Group Antigen Binding Adhesin A (BabA)

Mechanism of Action:

BabA attaches to Lewis b antigens and ABO blood group antigens found on the outer layer of stomach epithelial cells (Saikia et al., 2022). This robust attachment allows *H. pylori* to effectively colonize the gastric mucosa.

1. Prolonged Infection: The strong bonding provided by BabA guarantees that *H. pylori* stay closely connected to the gastric epithelium, resulting in enduring infection and the host cells being continually exposed to bacterial virulence factors such as CagA and VacA. This prolonged exposure contributes to sustained inflammation and damage to the epithelial cells, elevating the likelihood of carcinogenesis.

2. Inflammation and Immune Response: Adherence facilitated by BabA initiates the generation of pro-inflammatory cytokines like IL-8, which draws neutrophils and other immune cells to the infection site (Pereira et al., 2021). The subsequent persistent inflammation plays a crucial role in the advancement of gastric epithelial dysplasia and the onset of gastric cancer.

B) OipA (Outer Inflammatory Protein)

Mechanism of Action:

OipA is an additional protein located in the outer membrane of *H. pylori* and is responsible for its adherence to gastric epithelial cells. It also contributes to the initiation of inflammatory responses and the regulation of signaling pathways within host cells.

1. Induction of Inflammation: OipA has been demonstrated to boost IL-8 production, which aids in the attraction of immune cells and the maintenance of chronic inflammation. This prolonged inflammatory reaction fosters conditions that promote cellular harm, DNA mutations, and carcinogenesis.

2. Synergistic Effect with CagA: OipA frequently collaborates with CagA, a significant virulence factor, to interfere with host cell signaling pathways. This cooperation between OipA and CagA amplifies the cancer-causing capability of this bacteria by stimulating cell growth, blocking apoptosis, and promoting epithelial-mesenchymal transition (EMT), all pivotal processes in the progression of gastric cancer (Saxena et al., 2023).

Role in Gastric Carcinogenesis:

The binding of *H. pylori* to the stomach lining with proteins such as BabA and OipA promotes the ongoing infection and sustained immune reaction required for the development of gastric cancer. The inflammation triggered by these proteins plays a role in causing DNA damage, genetic instability, and the eventual conversion of healthy stomach cells into cancerous ones.

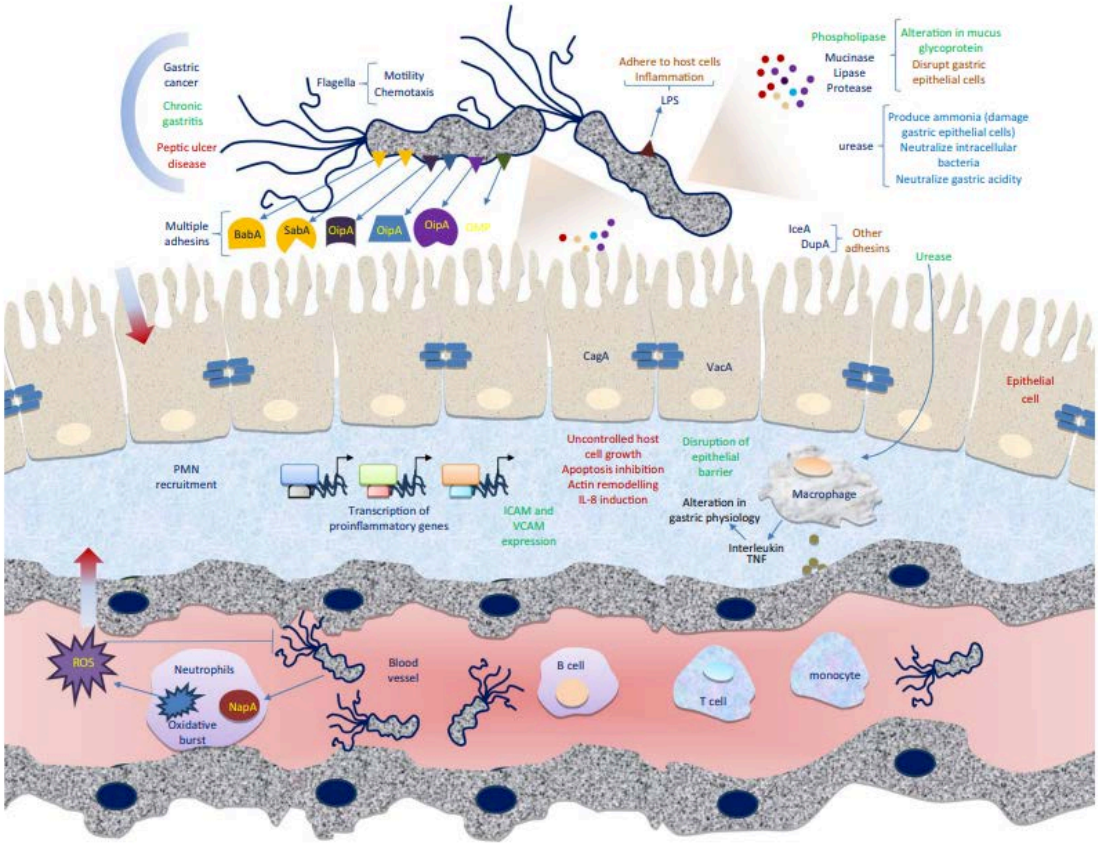

Fig. 3 Virulence summary of *H. pylori.* The colonization and onset of diseases and infections caused by *H. pylori* rely on four main stages: (1) adapting to the acidic environment of the

stomach lining, (2) moving towards the epithelial cells using flagella, (3) penetrating the epithelial cell barrier and attaching to specific receptors, and (4) causing tissue damage and other harmful health effects. In order to successfully colonize the host and establish an infection, *H. pylori* must be able to survive the acid in the stomach, bind to host cells (using a variety of adhesins), and release toxins that harm host tissues. For instance, the VacA protein aids in disrupting the epithelial barrier, while the urease can induce macrophages, leading to changes in gastric physiology. Several other effector proteins also play a critical role in the pathogenesis of *H. pylori*.

Chapter 3

Immune Evasion Strategies of *H. pylori*

3.1 *H. pylori* and Immune Evasion

H. pylori is a gram-negative bacterium that can cause a lifelong chronic infection of the human stomach. *H. pylori's* infection causes chronic gastritis, which can lead to atrophic peptic ulcers, gastric malignancies, and rarely extragastric conditions (de et al., 2022). The long-term colonization of the host by *H. pylori* is attributed to its ability to avoid various lines of host defense, which is called immune evasion (Zhou et al., 2022). There are multiple reasons why an infected host is unable to clear the bacterium. First, *H. pylori* presents a limited number of proteins to the human immune system that can be targeted by the host's immune response. Second, H. pylori is able to survive the acidic conditions in the stomach. Finally, in the case of eradication of the bacteria, the hyperproliferation of the gastric epithelium caused by infection predisposes the host to the development of *H. pylori*-induced pathologies (Larsen et al., 2020).

Thus, understanding the immune evasion mechanisms utilized by *H. pylori* may allow for more successful development of antibacterial treatments (Kuek & Lee, 2020). To colonize the host, live within the mucus lining of the stomach, and remain there for a lifetime, accumulating damage caused by the microbe requires a permanent combination of evasion measures of H. pylori with the host (Castro-Córdova et al., 2021). The colonization of the host is successively achieved through the interaction of bacterial factors with the host epithelial cells and by safety from the physical and chemical features of the gastric lumen (de et al., 2022). The strong but restricted inflammatory response enables the host to limit the load of H. pylori in the stomach without eradicating it (Zhou et al., 2022). If left untreated, *H. pylori* infection persists in the stomach in children throughout the life of the attending population. The infection can last for 7 to 10 days in the stomach when symptomatic disease requires evacuation of the micropyle. In contrast, the existence of *H. pylori* without eradicating the host's immune response in the stomach declines beyond 10 days (Larsen et al., 2020). The association of bacteria with its host primarily restricts the induced host's protective immune response (Kuek & Lee, 2020). The ability to cause a potent but minor immune reaction in the stomach over time would satisfy a necessary criterion from H. pylori (Castro-Córdova et al., 2021).

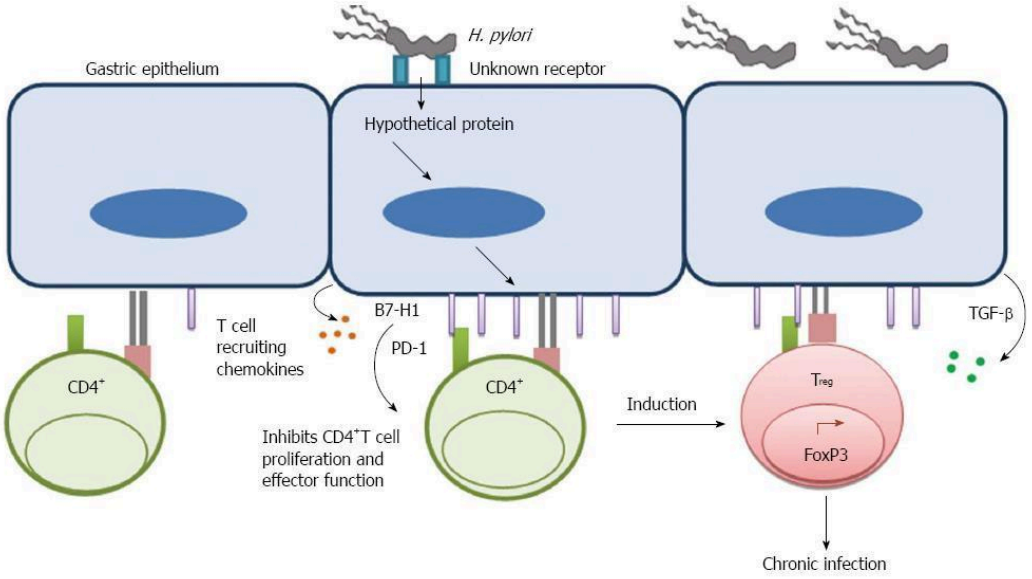

Fig. 4 illustrates how *Helicobacter pylori* use gastric epithelial cells (GECs) as intermediaries to suppress T cell activity. After binding to an unidentified receptor on GECs, *H. pylori* transfers a hypothetical protein, which triggers the expression of B7-H1 on these cells.

3.2 Evasion of Innate Immune Responses

H. pylori is a pathogen with a core genome of about 1,000 genes and a highly variable accessory genome. In particular, this bacterium possesses a large variety of virulence factors to interact with the innate and adaptive immune systems of the human host in order to evade the immune cellular response and survive in hostile environments (Behrens et al., 2020). While mechanisms for evading adaptive immunity are the best characterized, we focus on the recent knowledge concerning the several strategies used by *H. pylori* to avoid the main components of the innate immune response (Sijmons et al., 2022).

The innate immunity represents the first line of host defense and includes several types of nonspecific immune responses (Ishikawa-Ankerhold et al., 2024). One strategy used by *H. pylori* to escape from the immune system involves direct interaction with cells responsible for recognizing pathogens in the human digestive system. Although *H. pylori* is one of the few bacteria able to survive and grow in an acidic extracellular environment, it prefers the mucous lining of the stomach, where it tolerates the acidic internal compartments of the phagocytic cells (González et al., 2021). Hence, *H. pylori* is phagocytosed poorly and does not trigger the respiratory burst due to low proton conductance across the membranes of the early phagosomes (Prichard, 2022). Since antigens that are not presented on the surface of phagocytosed pathogens are not effectively presented to CD4+ T cells, the impairment of vesicular proton flux further decreases antigen presentation efficiency. Overall, inhibiting pathogen endocytosis and phagosome acidification are crucial strategies that contribute to H. pylori survival in phagocytic cells (Behrens et al., 2020).

3.3 Inhibition of Phagocytosis

H. pylori manipulates host cellular responses to evade ingestion by immune cells. Phagocytosis is a cellular process involved in the elimination of pathogens by professional cells of the immune system. Initially, *H. pylori* increases actin microfilament breakage in host cells through amphiphysin II (Niu et al., 2020). This results in hemidesmosome disruption, integrin endocytosis, and LPA-stimulated cell migration. When cells exposed to amphiphysin II are exposed to *H. pylori,* not only does the incidence of actin microfilament breakage increase, but also the ingestion of the bacteria occurs compared to the bacteria that do not inhibit actin microfilament breakage (Prashar et al., 2022). Moreover, when lymphocytes ingest H. pylori, they show the same migratory pattern (Fei et al., 2024).

We showed that on interaction with non-phagocytic cells, *H. pylori* binds to α5β1 integrin via the surface-exposed blood-group antigen-binding adhesin. In interaction with immune cells and the ECM, *H. pylori* binds to β2 integrins via the outer membrane protein (Zeng et al., 2022). This confers resistance to phagocytosis by immune cells but has a further role in immune evasion as β2 integrins bind to the ECM (Wei et al., 2024). Since phagocytosis is suppressed by *H. pylori,* this leads to slope clearance and chronic persistence in gastric mucosa. Techniques that improve phagocytosis may prove promising in the treatment of *H. pylori.* Both *H. pylori* and the host have evolved strategies in response to each other so that *H. pylori* avoids being ingested by immune cells. *H. pylori* has developed multiple immune evasion strategies because the disease persists in the majority of cases of *H. pylori* infection. We have shown that by activating cellular responses such as hemidesmosome disruption and the shedding of integrin, *H. pylori* is able to avoid being ingested by phagocytes (Niu et al., 2020).

3.4 Evasion of Pattern Recognition Receptors (PRRs)

Upon microbial contact, PRRs have a dual function as recognition molecules and mediators in delivering basic signals for the initiation and proper orchestration of innate and adaptive immune responses (Jeffery et al., 2022). Among the PRRs, Toll-like receptors (TLRs) and NOD-like receptor (NLR) families are the leading groups that have been reported to deal with *H. pylori.* Mechanisms for immune evasion by *H. pylori* towards TLRs or other PRRs have already been well illustrated (Mohammadzadeh et al., 2023). H. *pylori* also undergoes certain genetic variations to alter the structure of PAMPs; the membrane lipoproteins, oligosaccharides, or other PAMPs might be changed, or the unique PAMP ligands might be lost in the course of invasion (Kim, 2024). These bacterium-associated PAMPs would not be neutrally recognized by host PRRs.

The outcome of such genetic rearrangement or mutation of *H. pylori* PAMPs would finally result in an adapted regulatory response by the infected host, which makes the host tolerant of the bacteria or develops an ineffective immune defense reaction against them (Săsăran et al., 2021). Furthermore, it is logical to illustrate that some intrinsic bacterial TLR antagonists are also capable of modulating their associated signaling pathways (Liu et al., 2023). Once activated by PAMP, the PAMP-bound TLR would recruit a set of adaptors, including MyD88, TIRAP, TRIF, TRAM, and Mal, which are all bridging proteins located in the cytoplasm region of the plasma membrane, to further activate the downstream molecules of the MyD88-dependent pathway and MyD88-independent pathways. Further, the activation would contribute to the gene expression of pro-inflammatory cytokines, innate immune-related antimicrobial peptides, and other immune defense-related molecules required by the host.

3.5 Modulation of Adaptive Immune Responses

Adaptive responses develop in the long term, and, unlike the innate response, they can provide immunity against reinfection (Cheok et al., 2021). *H. pylori* has evolved a variety of mechanisms to dampen the effector activities of lymphocytes. T cells are an important effector population for the control of *H. pylori*, and *H. pylori* has evolved mechanisms to dampen T cell responses (Ailloud et al., 2021). A major aspect of H. pylori immune evasion strategies focuses on the modification of T cell responses. Various effector T cell populations such as Th1, Th17, and Treg appear to be affected by *H. pylori*. When naive T cells activate, they enter into a rapid cell division program. These T cells then differentiate into effector T cells or memory T cells, which support long-term immune protection (Zeng et al., 2022). These responses require the activation of co-stimulatory receptors such as CD27 that propagate and maintain T cell activation. But activation of these co-stimulatory receptors is impaired in *H. pylori*-specific T cells, resulting in low effector function and impaired T cell responses (Capparelli & Iannelli, 2022). Due to the impairment of T cell activation and effector functions, *H. pylori*-antigen specific T cells are detectable in large quantities but are unable to go to the tissues and eliminate the bacteria. The generation of a well-adapted T effector response is inhibited, which masks pathogens and results in low-grade chronic infections. Presentation of antigens to T cells is commonly disturbed during CM via different mechanisms to evade immune clearance (Fan et al., 2024). The sophisticated pathway of antigen uptake and presentation is the crucial mechanism to identify the potentially dangerous activating and effector function of adaptive immune responses. Overall, *H. pylori* has successfully evolved many strategies to evade and alter the host's immune system and has developed into an attractive candidate to investigate immune modulation through CM for the past few decades. The outcome of CM alters the importance and activation of adaptive immune systems. The provision of a suitable CM combined with immunization methods can reduce these limitations and offer a challenge in vaccination and immune therapies.

3.6 Suppression of T-cell Responses

T-cell-orchestrated adaptive immune responses play important roles against many intracellular bacterial infections, whereas *H. pylori* is an obligate extracellular pathogen. Early evidence of *H. pylori*-mediated suppression of T-cell responses was based on the suppression of T helper (TH) -1 and class switching Th2 cytokines, which is an ineffective systemic acquired immunity effect. In contrast, the TH1 and Th17 cells are major players in orchestrating antimicrobial immunity at the interface of the microbe and host. The new evidence about TH1 is required to differentiate chronic infections from long-term asymptomatic carriers of H. pylori. In this mini-review, we discuss the status of H. pylori-mediated suppression of T-cell responses and its immunopathologic consequences.

Further delineation of the mechanisms of *H. pylori* T-cell immune evasion strategies is important for identifying new targets to enhance T-cell responsiveness against *H. pylori* and better disease management. Since *H. pylori* is an extracellular pathogen and TH1 and TH17 cell activities are required for extracellular pathogen eradication and tissue-protective immunity, several *H. pylori* immune evasion mechanisms have been identified specifically to dampen TH1 and TH17 CD4 T-cell activity (González et al., 2021; Fan et al., 2024). *H. pylori* has been found to subvert a variety of signaling and regulatory events in T lymphocytes, using both cell-contact-dependent and independent mechanisms. Briefly, *H. pylori* alone or in combination with other cells resulted in defective T lymphocyte activation, proliferation, and cytokine secretion in infected individuals (Kim, 2024). The T-cell inhibitory concentration of TGF-beta, IL-10, indoleamine 2,3-dioxygenase, and CD274, accompanied by T-cell receptor signaling disruption, has increased in vitro, suggesting they are mainly involved in the H. pylori immune evasive mechanism against T lymphocytes (Oster et al., 2022). Although more mechanisms need to be elucidated, H. pylori infection progression typically begins with an evolving TH1 response, eventually leading to an ineffective TH1 and TH17 response, which often happens concurrently with chronic phase infections. Failure to eliminate *H. pylori* infection from the individual may favor the development of non-communicable diseases (NCDs) and some rare diseases, including morbidity and/or mortality. Both are exacerbated by the multi-pathological sequelae (Bimczok et al., 2020).

3.7 Disruption of Antigen Presentation

Antigen presentation is crucial to alert the adaptive immune system against invading pathogens. Antigen-presenting cells (APCs), including dendritic cells (DCs) and macrophages, take up antigens, degrade them into small peptides, and present them on the cell surface in combination with major histocompatibility complex (MHC) encoded molecules (Zhang et al., 2020). Once inside the host, H. pylori encounters primarily resident macrophages and DCs. However, the frequency of APCs in the lamina propria is higher than in the gastric epithelial layer, and some H. pylori-infected people lack obvious DC inflammation (Chichirau et al., 2020). The patterns of DCs' dynamic trafficking and differentiation are likely to modify the adaptive immune response following gastric infection. Consistent with that, H. pylori has been described to have the capacity to alter the above mentioned DC functions towards a more tolerogenic itinerary. The phenotypic alteration includes the expansion of tolerogenic monocyte-derived macrophages, downregulated CCR7 allowing retention of DCs in the inflamed gastric mucosa, and low production of IL-12 and high production of IL-10. As DCs distribute to secondary lymphoid tissues such as the spleen, we can hypothesize that gastric-infected DCs recruit tolerogenic DCs for systemic distribution due to myelopoiesis in the spleen (Oster et al., 2022).

The mechanism by which *H. pylori* could reduce anti-H. pylori T-cell responses by impairing the capability of APCs to deliver antigens to the effector T-cell using multiple strategies. First, the surface antigen structure of *H. pylori* antigens might not efficiently bind to TLR, thus preventing APCs from responding to *H. pylori.* Secondly, since H. pylori is protected by a glycan coat of LPS and can also hide other surface antigens with shielding glycans, which are not shed sub-products of metabolism and cannot be released into the MHC II loading pathway (Zhang et al., 2020). Therefore, *H. pylori* is not efficiently presented to the extracellular MHC II presentation pathway. Thirdly, *H. pylori* can also avoid vacuolization into the MHC II loading path. Helicobacter specifically promotes deglycosylation of the intermediate sodium pH of a vacuolar environment, which makes it impossible for a hydrogen ion-driven ATP pump to pump protons into the vacuole. This implies that the antigen itself is transported across the vacuole into the default MHC I loading path. Hence, a few HSP60 *H. pylori* antigens will be presented by DCs to the MHC I cross-presentation path (Sijmons et al., 2022).

3.8 Role of Chronic Inflammation in Immune Evasion

Persistent infections frequently result in chronic inflammation. *H. pylori,* as a colonizer of the stomach, is a major contributor to chronic inflammation. Chronic inflammation not only causes substantial tissue damage characterized by the loss of glandular structure and replacement by fibrosis, but it also functions as a major driver of carcinogenesis through the induction of genetic and epigenetic changes in host cells. Chronic inflammation also complicates immune effector functions, resulting in an exhausted phenotype. Thus, to persist, *H. pylori* has developed several strategies to shape the immune response in the gastric environment (Zhang et al., 2020).

H. pylori has been demonstrated to preferentially position itself within the gastric glands, where it can reside either extracellularly along the stomach's inner lining or intracellularly within either the mucous layer or the mucosa from the basolateral membrane of the epithelium to the lamina propria (Yang et al., 2021). Importantly, the bacteria residing on the sites lining the inner part of the stomach are not in direct contact with the lumen. Although contained within glands, these H. pylori bacteria perpetuate chronic inflammation, particularly within the lamina propria. The persistent chronic inflammation triggered by *H. pylori* not only provides a protective niche for its survival by nebulous humoral and cellular immune effector functions including facilitating cytotoxic T cells but also interferes with the generation of protective cellular immunity (Kim, 2024). Consistently, high bacterial loads are usually observed in individuals showing substantial lymphocyte infiltrates and relatively high pro-inflammatory cytokines in the gastric lamina propria (Denic et al., 2020).

H. pylori-infected gastritis is characterized by the ongoing recruitment of immune cells, quite distinct from the protective roles of acute inflammation. These recruited immune cells add to the overall milieu of on-site cellular interactions, enzymes, growth factors, and nutrients, which in turn assist the bacterium to survive. The development of gastric MALT lymphoma requires a clonal expansion of B cells by H. pylori-presented antigens, along with the continuous stimulation provided by the persistent inflammation content. Also, strategies like inducing T cell apoptosis, anergy, and inducing Tregs would indirectly make the host ideal for long-term *H. pylori* survival. Interestingly, the on-site cytokines and chemokines produced due to ongoing inflammation support epithelial repair and regeneration and prevent H. pylori-incited

inflammatory initiations near the glandular base from reaching the luminal surface of the stomach and causing acidic dysregulation. Hence, ongoing inflammation is also important for *H. pylori* in terms of disease pathogenesis (Sun et al., 2022).

3.9 Persistent Inflammatory Environment

Exposure to pathogen-associated molecular patterns (PAMPs) and secreted effector proteins triggers the innate immune system. The production of antimicrobial factors, complement proteins, and the recruitment of immune cells comprise a host's protective responses (Zeng et al., 2022). Importantly, acute inflammation also instructs the ensuing responses of the immune system, which are essential for pathogen clearance (Zhang et al., 2022). Inflammation typically results in resolution and creates an environment of tissue repair, promoting the recovery of the threatened sites. In contrast, *H. pylori* evolved to exploit the protective inflammation to persist in its niche, the mucus layer, and to impact tissue differentiation in opposition to other microaerophilic pathobionts dwelling in the same niche (Sigal, 2020). A signature of H. pylori-associated pathologies is the constant recruitment of immune cells to the gastric mucosa. When inflammation is sustained or exaggerated, it is called a chronic inflammatory environment (Serrano et al., 2021). Indeed, H. pylori* infection was found to drive a persistent inflammatory environment over decades in a sufficient number of patients to claim a historical record of ulcer disease and Atlantic-type adenocarcinoma (Prashar et al., 2022). The molecular crosstalk between H. pylori and the immune cells, the amounts of immune cells, or which cytokines predominantly influence the pathophysiological changes, conclude in a different spectrum of chronological pathologies. Most research on the interaction of H. pylori with the immune system was done in humans, while murine models of *H. pylori* infection mostly recapitulate the H. pylori-induced inflammation in the mouse rather than the clinical spectrum in humans. By maintaining inflammation, *H. pylori* is not only able to evade immune clearance but possibly contributes to further damage. Hence, the interplay between inflammation and immune evasion is critical for understanding chronic *H. pylori* infection. Clearing inflammation has the potential to resolve and even prevent *H. pylori*-associated pathologies.

3.10 Pro-inflammatory Cytokine Production

Cytokines are critically important in the regulation of the immune response. Their crucial role in maintaining the balance between proinflammatory activity, humoral immunity, and resolution of infection stems largely from their ability to communicate with cells in the immediate vicinity of their release, as well as to act in an endocrine manner on remote cells and tissues exposed to low levels of circulating cytokines (Zuo et al., 2021). Following the discovery of *H. pylori*, pro-inflammatory cytokines including IL-1β, IL-6, IL-8, and TNF-α were found to be highly produced in areas of the stomach colonized by *H. pylori*, without which very little cytokine is produced (Miller & Williams, 2021). The fact that very little cytokine is produced in the stomach during acute *H. pylori* infection, despite the high concentrations of bacteria present, provided the first clues that *H. pylori* may dampen the local immune response. The pro-inflammatory cytokine response during *H. pylori* infection and vaccination are summarized (Zhang et al., 2022). The effects of pro-inflammatory cytokines on the activities of immune cells are complex, but the combined activities of IL-1β, TNF-α, and IL-6 act to upregulate the expression of adhesion molecules on endothelial cells, leading to an influx of neutrophils and other phagocytes (Malfertheiner et al., 2023). Neutrophils and other phagocytic cells expressing a wide range of pattern recognition receptors express the C-type lectin dectin-1, which responds to β-glucans and is key in the facultative intracellular targeting of scavenger receptor-expressing macrophages and neutrophils. Recent studies have been pivotal in revealing the intracellular escape of H. pylori and highlighting that the presence of phagocytes can be disadvantageous to the host on occasion (Faass et al., 2023). The cellular responses of the largest contributions to the pro-inflammatory immune reaction infected by *H. pylori* are implicated in the immune evasion strategy of *H. pylori*, as discussed below. The importance of cytokines in tissue injury stemming from the overproduction of pro-inflammatory cytokines is included in the discussion. Failing the effective removal of *H. pylori,* the overproduction of pro-inflammatory cytokines is substantially contributing to the persistence of chronic distress and associated pathogenesis. At the end of this review, we discuss the development of therapeutic strategies that focus on modifying the cytokine response (Faass et al., 2023).

Chapter 4

Mechanisms of Gastric Carcinogenesis Linked to Immune Evasion

4.1 Gastric Carcinogenesis and Immune Evasion

In the majority of human malignancies, the acquisition of various cancer characteristics occurs gradually over time, leading to a spectrum of tumors that can range from relatively benign and easy-to-treat forms to highly aggressive tumors that pose a significant threat to health. This progression toward malignancy is not merely a result of genetic and epigenetic alterations alone; it is concurrently accompanied by substantial modifications within the host's immune system. Such complex mechanisms have captured increasing attention in the scientific community, focusing sharply on understanding how unique immune features could potentially be targeted (Seeneevassen et al., 2021). This understanding may serve dual purposes: aiding in the early detection of cancer as well as enhancing therapeutic approaches (Yeoh & Tan, 2022). Gastric cancer, notably, stands as the fourth most commonly diagnosed malignancy globally and is recognized as the second leading cause of cancer-related deaths (Liabeuf et al., 2022). It is widely comprehended that this form of cancer evolves from a complex interplay of environmental and genetic influences that together facilitate immune evasion, allowing the cancer cells to escape the body's natural defense mechanisms (Ebrahimi et al., 2020).

Despite a noted decrease in the overall incidence of gastric cancer in some populations, the development of personalized therapies and innovative immune-based treatments offers tremendous potential for overcoming the challenges posed by its current poor prognosis (Gullo et al., 2020). Nevertheless, as of now, the application of immunotherapy for gastric cancer has proven to be markedly ineffective, underlining the urgent need for continued research and novel approaches in this vital area of cancer treatment. The human immune system has multiple tumor-antagonistic properties that can often prevent the development of a clinically relevant neoplasm. However, in some cases, tumors develop immune evasion mechanisms that corrupt the ongoing immune response. Immune evasion can be operational at various steps (Tauriello et al., 2022). In the first step, it may subvert the host immune surveillance by preventing the recognition of malignant cells by the immune system. After that, some tumor cells may promote immune tolerance, allowing them to grow and finally escape immune effector mechanisms. Mechanisms of immune evasion are characterized by two major strategies (Kotsafti et al., 2020). First, tumor cells may lack both tumor-specific antigens and co-stimulatory signals needed for the initiation of anti-tumor effector immune responses. Additionally, the tumor microenvironment itself may further lead to the anergy or deletion of tumor-infiltrating effector

immune cells. In solid cancers, the latter process can be facilitated by chronic tumor exposure to immune cell-derived cytokines (Cervantes-Villagrana et al.2020).

4.2 Gastric Cancer

Chronic inflammation and the pathological conditions associated with it, such as chronic infections, sustain host cell signaling pathways that are involved in many aspects of cell transformation. Understanding the molecular mechanisms employed by *H. pylori* could be helpful in stratifying the stage at which *H. pylori* is involved in the sequence from early gastric lesions to gastric cancer and could have implications in adjuvant therapy (Piscione et al. 2021). In order to monitor such changes and learn about the critical alterations in a given individual, cellular assays such as the image transformation matrix, the genetic instability assay, and the detection test have been designed. *H. pylori* is able to orchestrate a variety of effector pathways that allow it to avoid immune clearance, chronically persist within the gastric mucosa, and adapt to different pathogens and hosts (Senchukova et al., 2021).

The association of *H. pylori* with the development of gastric cancer has been underpinned by several epidemiological cohort studies. Furthermore, the relevance of the inflammatory microenvironment in mediating tumor progression is underpinned by the fact that long-term use of *H. pylori* proinflammatory co-treatment is able to drive gastric tumor development on its own. Hence, it is not only the ability of *H. pylori* to promote proinflammatory pathways of signal transduction, while driving transformation through functions, or polymorphisms, or a specific genotype that will funnel subsequent downstream events, but this cascade is also associated with poor prognosis. Finally, treating *H. pylori* in a timely fashion, based on its underlying etiopathological causes, is expected to stratify and modulate the risk of developing specific extra-gastric cancers by reducing the associated proinflammatory load (Tempera et al., 2022).

4.3 Immune Evasion in Cancer

A large quantity of scientific literature over the past half century has documented that the immune system can recognize and eliminate cancer cells. However, a growing body of work over the past 20 years has helped to delineate many of the strategies that tumors can employ to escape detection and destruction by the immune system. An overview of many of these mechanisms will be provided herein. One process that is exclusively regulated at the level of the cancer cell is the process of antigen presentation and reactivity of the host immune system. Through numerous described mechanisms, tumor cells can alter their antigenic profile to escape immune recognition. However, tumors can also establish immunosuppressive microenvironments through a combination of local immunosuppressive factors, recruitment of immunosuppressive immune cells, and establishing structural barriers to immune reactivity. These defenses are unleashed to either achieve homeostatic tissue repair or can also be co-opted by rapidly expanding pathological tissue masses such as tumors (You et al.2021).

Furthermore, there is evidence that immune evasion can lead to cancer progression and metastasis. The use of targeted therapies in cancer management has been an important part of recent cancer treatment outcomes. However, immunotherapy using immune checkpoint inhibitors from a host-tumor relation perspective may have contributed to novel advances in a few immune-oncology pivotal clinical trials (Tauriello et al., 2022). To date, new classes of drugs are being developed, and in this regard, different organizations across the globe are investing in identifying mechanisms underlying immune evasion in patients with different cancer types. Overall, ignoring immunobiology can influence the rate of progress observed in the field of oncology (Garner & de Visser, 2020). Speakers at each conference or public event are encouraged to avoid neglecting the importance of understanding immune evasion mechanisms for cancer progression as well as treatment. In particular, it is frequently recommended to incorporate mechanisms of immune evasion in their programs. These would then lead to future basic, translational, and clinical investigations designed to take into account the inhibitory molecules and targets where they matter based on host-tumor relations (Giordano et al.2020).

4.4 Stepwise Progression of Disease

Gastric cancer is the fifth most common cancer and the fourth leading cause of cancer-related deaths, making it one of the most important global health problems. Despite showing a decreasing trend over the last few decades, the highest age-standardized incidence is still observed in Eastern Asia, Central and Eastern Europe, and South America, while the lowest rates are in Eastern Africa (Joshi & Badgwell, 2021). There is about a twofold higher incidence rate in men than in women (Wang et al., 2021). The pathophysiology of gastric cancer is not fully understood, but it is generally considered to be a multistep process characterized by the transition of normal gastric epithelium to chronic gastritis, atrophic gastritis, epithelial metaplasia, dysplasia, and finally invasive tumors (Oya et al., 2020). A variety of different factors can promote this transition, including multiple genes, signaling pathways, and cell types (Li et al., 2020). The prognosis of gastric cancer is closely related to the stage of the tumor at the time of diagnosis. Currently, imaging techniques such as endoscopy and gastroscopy are considered to be the main methods of diagnosis (Joshi & Badgwell, 2021). However, since early-stage patients are usually asymptomatic or present with nonspecific upper abdominal signs and symptoms such as nausea, low appetite, weight loss, and early satiety, most cases are diagnosed after metastasis (Wang et al., 2021). An accurate diagnosis is essential for the prognosis, and therefore surgical management is the primary treatment (Oya et al., 2020). Patients with limited regional spread receive adjuvant chemotherapy to eradicate residual disease, but advanced-stage patients are not eligible for this treatment (Li et al., 2020).

In recent years, improved understanding of the molecular features of this disease has emerged, and research on targeted drugs for patients with less common molecular mutations is progressing (Joshi & Badgwell, 2021). The international guidelines suggest molecular profiling for patients at advanced stages (Wang et al., 2021). Given that about 90-95% of tumors occur sporadically, in the absence of a clear family history, and the latency between exposure to carcinogens and the appearance of the disease, the most impact could come from prevention (Oya et al., 2020). In this context, it is important to understand the pathophysiology of the factors that favor the development of gastric cancer and when additional public health measures may be needed (Li et al., 2020).

4.5 *H. pylori* Infection to Gastric Cancer

Although the incidence of gastric cancer is decreasing, it remains one of the most frequently diagnosed and deadliest malignancies worldwide. This trend appears to be associated with the reduction in certain cancers, thus suggesting that changes in environmental or behavioral risk factors, such as diet, obesity, and reduced prevalence, are involved in this declining pattern. Chronic infection is etiologically associated with the subsequent development of gastric cancer. It has developed a strong capacity to survive in the hostile gastric conditions, especially the acid environment, and colonizes the stomach in more than half of the human population. The sustaining infection shapes the composition of the gastric microbiota and correlates with an increase in pro-inflammatory cytokines and regulatory T cell numbers. Persisting inflammation gradually affects the multifunctional physiological processes in the host. Infection determines the host and microbial factors (Zhu et al., 2022). Among these, the presence of certain bacterial genes and their products, the host genetic background, differential gene expression, and immune evasion are the modulators of the outcome of infection and pathology. Infection is associated with a deep infiltration of the gastric mucosa by neutrophils and monocytes and a mixed adaptive response due to the expansion of Th1 cells. In the initially infected individuals, the inflammation is usually restricted to the antral mucosa, as corpus-predominant inflammation only occurs in a portion of infected individuals. It induces DNA damage in the host cells, alters the mitochondria, and enhances the rate of apoptosis of gastric epithelial cells. Gastric colonization is needed for atrophic gastritis development, with a mild but marginal association between bacterial load and loss of gastric glands. Personal preventive procedures, such as early detection through endoscopic biopsies and eradication of bacterial infection, are crucial in the framework of "cancer-preventive" strategies (Nasr et al.2020).

4.6 Contribution of Immune Evasion

H. pylori infection has been shown to remain active for the lifetime of the human. Activation of neutrophils and release of reactive oxygen and nitrogen species generate a vicious cycle and lead to sustained high levels of inflammation without resolution. When the levels of immune activation drop at a mucosal site, it is most often an indicator of non-responsiveness or irreversible damage. Mice that lack T cell signaling pathways never develop inflammation and never succumb to infection. Intestinal-type gastric carcinoma is an inflammatory carcinoma, meaning that there is sufficient inflammation and activation, and that the immune balance is potentially irregular. Furthermore, *H. pylori* infection can shift the effector cytokine profile from Th1 to a mixed pattern of Th1, Treg, and Th17 effector cells (Ucaryilmaz Metin & Ozcan, 2022).

One of the hallmarks of precancer in gastric cancer is the influx of Treg into the mucosa. Mice that have T regulatory cells also go on to develop malignancy faster than those that do not. Only after mucosal invasion do epithelial stem cells become oncogenic. It is the increase in stem cell proliferation that leads to increased stem cell mutation potential through a better chance of chemotherapy errors and tumor invasion and spread. Significantly, one of the ways that *H. pylori* infection can lead to an increase in DNA error rates is through immune evasion. The role and interplay of chronic infection plus immune evasion can give ample time to evolve mechanisms of rapid and systemic immune escape, including the ability to trigger polyclonal T cell tolerance and apoptosis in T cells. Furthermore, this immune escape mechanism itself can lead to chronic infection due to the shift in immune responses to the adaptive phase of immune activation or resampling (Baj et al.2020).

4.7 Impact of Chronic Inflammation on Carcinogenesis

Chronic inflammation has long been recognized as a "hallmark of cancer." Chronic inflammation operates as a double-edged sword: on one hand, it actively promotes clonal evolution and tumorigenesis by offering numerous growth factors and cytokines, provoking cell proliferation, mutating oncogenes, or deactivating oncosuppressors by direct damage, and inducing angiogenesis (Yang et al., 2023). On the other hand, chronic inflammation can also activate strong immune responses that act to counteract tumor progression and mediate tumor rejection (Tryapitsyn et al., 2021). Chronic inflammation and its organic dysregulation are vasculolymphostroma mediators, acting through an order of recognition and reaction elements that are themselves targets of damage (Li et al., 2020). These same elements are also responsible for counteracting extensive tissue damage and restoring homeostasis (Kotelevets & Chekh, 2020). The chronicity of inflammation unchains a series of pathological conditions, and one of the most severe is cancer. Chronic inflammation plays at least three roles in carcinogenesis. First, inflammation causes DNA damage by promoting the recurrent generation of oxygen and nitrogen free radicals, and several products of lipid peroxidation, overproduction of some phospholipids, decomposition of hemoglobin, and exaggerated or ectopic accumulation of iron or some transitional elements (Yang et al., 2023). Second, inflammation promotes somatic mutations in the p53, K-ras, and B-catenin genes associated with gene disarrangement, and a mutator phenotype in which those genetic aberrations are extremely rare (Tryapitsyn et al., 2021). Third, inflammation promotes cell proliferation. Hyperproliferation of mesenchymal, stromal, and inflammatory cells results in an abnormally vast potential for mutation (Li et al., 2020). Inflammation-induced mutations that are the initiators of cancer might be entirely distinct from mutations that drive clonal evolution and are essential processes in carcinogenesis (Kotelevets & Chekh, 2020). For example, the NF-kB signaling pathway is mainly affected by inflammation and is constitutively activated in many types of human tumors (Yang et al., 2023). Previous clinical and epidemiological studies have indicated that chronic gastritis is the precancerous state of stomach adenocarcinoma (Tryapitsyn et al., 2021). If *H. pylori* infection is left untreated for a long period, about 10% of infected people will develop gastric cancer (Li et al., 2020). Therefore, prevention of chronic inflammation may help to reduce the incidence of gastrointestinal cancer (Kotelevets & Chekh, 2020). However, it is not clear which anti-inflammatory strategies can effectively block the carcinogenic process caused by chronic

inflammation. A molecular approach to the link between inflammation and gastric cancer may provide new leads for clinical research (Yang et al., 2023).

4.8. Role of Chronic Inflammation in DNA Damage and Mutations

Persistent chronic inflammation is a recognized causal factor in the initiation of neoplastic transformation, acting as a tumor promoter through immunosuppressive mechanisms. Some of the mechanisms underlying this effect were studied, but much is still unknown (Afify et al., 2022). A consistent body of evidence suggests that chronic inflammation due to infectious agents or other factors leads to increased DNA damage and mutational burden.

Mechanistically, inflammatory cells can contribute to the production of reactive oxygen and nitrogen species, which can lead to the formation of DNA lesions and mutations (Neganova et al., 2021). The genomic damage inflicted by chronic inflammation is repaired through conserved molecular machinery, which, when absent, drives the maintenance of genomic integrity through apoptosis (Nigam et al.2023).

Damage can also be repaired in an error-prone manner by base excision repair enzymes, thus leading to the accumulation of mutations in DNA. In particular, this may result in mutations in regulatory genes in cytotoxic T lymphocytes, thus blunting the responses to pre-existing tumor clones or promoting escape from the surveillance of the immune system. Once failed, the repair of a mutation is expected to be transmitted to daughter cells, leading to cancer over time and being involved in carcinogenesis (Neganova et al., 2021). Inflammation and associated DNA damage can potentially provide biomarkers for early detection in some cancers, and, more importantly, targeting the amount of inflammation may facilitate the prevention of cancer in the first place. Summarizing, people studying mechanisms of gastrointestinal inflammation have struck upon some probable facilitators of carcinogenesis, although new findings are still being collected (Yu et al.2022).

4.9 Disruption of the Tumor Microenvironment

In addition to the genetic and epigenetic events occurring in cancer cells, tumor development, and progression are also affected by the interactions between cancer cells and their surrounding environment. The tumor microenvironment is mainly composed of fibroblasts, endothelial cells, pericytes, immune cells such as myeloid-derived suppressor cells, tumor-associated macrophages, regulatory T cells, and extracellular matrix components. All these cellular and noncellular factors contribute to creating a favorable environment for the growth, spread, and survival of cancer cells, supporting the formation of a pre-metastatic niche (Yuan et al., 2023). Finally, by promoting angiogenesis and lymphangiogenesis, the tumor microenvironment ensures a sufficient blood and nutrient supply for cancer cells (Henke et al., 2020). In addition, these entities synthesize the extracellular matrix, a scaffold-like net of fibrillar proteins such as collagen fibers, glycoproteins, and proteoglycans (Lei et al., 2020).

The tumor microenvironment is pivotal in cancer development. The dynamic interplay between cancer cells and the immune system has been highlighted, and its role as an essential clue in the acquisition of tumoral immune escape by current research. In the earlier and later stages of carcinogenesis, this crosstalk is mainly executed by various soluble factors, such as cytokines, chemokines, extracellular matrix modulation, and growth factors. In the last decade, interest has also increased in the study of extracellular vesicles as mediators for tumor plasticity and resistance to therapy (Dymicka-Piekarska et al.2021). Altogether, the relocation of immune cells and their modulation induces a plethora of immunosuppressive events. Given its crucial role in controlling gastric cancer chemo-immune responses, the tumor microenvironment needs to be explored in order to create novel and more effective therapy methods. Therapeutic strategies were aimed at hampering interactions between cancer cells and tumor microenvironment components, thus resulting in an amplification of conventional chemo-radiation/immunotherapy efficacy, and patient outcomes (Desbois & Wang, 2021).

4.10 Immunosuppressive Microenvironment

The hostile microenvironment within gastric tumors is not just a product of immunogenic pressures, but also an orchestrated strategy for the development of an immune-tolerant niche, which is crucial in the defense against anti-tumor immunity. A variety of mechanisms underpin this survival tactic. In the early stages of a tumor, tumor cells secrete molecules that inhibit the body's natural widespread immune response, thus allowing the development of a distinct immunosuppressive nidus. These factors can modulate the function of immune cells, recruit them into the tumor stroma, or stimulate them to produce their own pro-tumor and immunosuppressive factors (Kotsafti et al., 2020). Moreover, their interactions with the metabolically modified tumor environment shape the immune landscape of the tumor, supporting its growth. Tumor immune evasion is mainly attributable to the dynamic relationship between immune and tumor cells. T regulatory cells can eliminate tumor-reactive T cells from the tumor microenvironment, while myeloid-derived suppressor cells can block T cell functions partly by producing nitric oxide (Kim & Cho, 2022). M2 macrophages are also present and secrete suppressive cytokines. Tumor cells can produce an array of immune checkpoint molecules and secrete cytokines that potently suppress T cell proliferation and interferon elaboration. Therapeutically, overcoming this status quo might restore anti-tumor immunity. Despite the overall survival benefits of checkpoint monotherapy, it is the rare subset of patients who develop complete or durable responses (Zhang & Zhang, 2020). The full benefit is more often seen when immune infiltrates are suppressed. Such data highlight the challenges posed by the paradoxical state of immunosuppression. Strategies aimed at breaking the immunosuppressive tumor microenvironment and restoring anti-tumor immunity may lead to novel approaches that are clinically economic and translationally effective. This highlights the importance of gaining a deeper understanding of the intricate interplay that prevails within the tumor (You et al., 2021).

4.11 Contribution of Immune Cells in Tumor Growth

An effective immune system serves as a primary defense mechanism against cancer initiation. Nevertheless, as tumor cells evolve, they can hijack immune cells and use them for their growth and survival. Growth, development, and tumor resistance are influenced by different types of immune cells (Seliger & Massa, 2021). For example, T cells deficient in secreted molecules such as cytotoxic chemicals, cytokines, and growth factors play a supportive role in inhibiting angiogenesis and causing apoptosis. However, T cells can suppress cytotoxic immune cells and promote inflammation. Furthermore, they also stimulate tumor growth. Macrophages are a good source of growth factors necessary in tumor biology. For instance, tumor-associated macrophages produce growth factors such as VEGF, FGF, EGF, and PDGF. Human monocytes differentiate into dendritic cells in response to various hematopoietic growth factors, including GM-CSF (Brunell et al., 2023). Dendritic cells are also involved in the activation of T cells and other immune responses, presenting antigens to T cells. In the context of tumors, macrophages and dendritic cells contribute to inflammation and adapt to the immune response, participating in the inhibition of tumor proliferation. Tumor cells can suppress immune activity by presenting antigens to cytotoxic T cells, modulating cytokine production, and increasing Treg populations (Weverwijk & De, 2023). The biology of escaping an immune attack in the tumor microenvironment is very complicated, but the activation of immune responses can predict a better clinical outcome. Therefore, tumor immunity is important for understanding. (Lin et al., 2022) Tumorigenesis is influenced by complex interactions between the immune and adaptive immune systems. An extensive cancer genome study led to the emergence of immunotherapies, using the patient's T cells to target tumor antigens and express immune checkpoints (Balta et al., 2021).

Conclusion

All in all, there is a multifaceted interplay between *H. pylori* and gastric cancer that emphasizes the vital role that chronic infection plays in the development of this illness. About half of the world's population has *H. pylori* colonizing their stomach mucosa, and it has evolved sophisticated defense mechanisms to elude the host's immune system. The overproduction of pro-inflammatory cytokines and immune cell infiltration that result from this persistent infection cause chronic inflammation, which can interfere with normal stomach physiology and encourage the conversion of gastric epithelial cells into malignant cells. The data in this analysis highlights that although stomach cancer incidence is on the decline, it is still a major public health problem, especially in areas where the prevalence of *H. pylori* is high. Comprehending the genetic, environmental, and behavioral factors that contribute to this infection is essential for developing effective prevention and treatment strategies.

Furthermore, understanding how *H. pylori* avoids immune response provides great potential for the development of new therapies. Knowledge of the immune environment in gastric cancer is changing, and it appears that it may be possible to shift focus away from simply treating the tumor and instead look towards targeting the inflammatory environment as well as the immune system itself. An understanding of these abnormalities concentrated from *H. pylori* infections could help the inventors to come up with new strategies that will not only help eradicate the bacterium but also stop its evolution towards gastric cancer. Incorporating molecular profiling and targeted therapies into the clinical setting might advance the disease management of patients at high risk for developing gastric cancer. Although in the process of throwing more light into the gastric cancer causation by *H. pylori* the need to direct research and new public health policies to this problem should be the main focus, with the background of prevention of emergence of the disease which is advanced gastric cancer burden and bottom line patient’s outcome.

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