Pathogenesis of *Helicobacter pylori*

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Helicobacter pylori (*H. pylori*) is a Gram-negative bacterium that colonizes the gastric mucosa and is associated with various gastrointestinal disorders. *H. pylori* is a pervasive pathogen, infecting nearly 50% of the world's population, and presents a substantial concern due to its link with gastric cancer, ranking as the third most common cause of global cancer-related mortality.

pathogenesis virulence factors

1. Introduction

Helicobacter pylori, a ubiquitous, microaerophilic, spiral-shaped, Gram-negative bacterium residing in the human stomach, has profoundly impacted the landscape of gastroenterology and infectious diseases since its discovery in 1982 [1]. Before its identification, peptic ulcer disease was primarily attributed to stress and dietary factors, fundamentally altering researchers' understanding of its etiology. This revolutionary discovery earned Barry J. Marshall and Robin Warren the Nobel Prize in Physiology or Medicine in 2005 and laid the foundation for a comprehensive investigation into *H. pylori*'s role in various gastrointestinal disorders [2]. As the scientific community has continued to unravel the complexities of this pathogen, the field of *H. pylori* research has witnessed remarkable advancements. *H. pylori* colonizes the gastric mucosa of approximately half the world's population, making it one of the most prevalent human infections [2]. Its ability to establish a persistent and often lifelong infection in the stomach lining has earned it a reputation as a formidable pathogen. The bacterium's remarkable adaptability to the acidic and inhospitable gastric environment has led to a plethora of host responses and pathological outcomes [3][4]. From its initial association with peptic ulcers, researchers's understanding has expanded to include its role in gastritis, duodenal ulcers, gastric cancer, mucoid-associated lymphoid tissue (MALT) lymphoma, and a range of extra-gastric conditions, including neurological, ocular, hematologic, cardiovascular, and dermatological diseases, which afflict millions worldwide and have substantial economic and healthcare burdens [4][5][6]. The complex interplay between *H. pylori* and its human host have spurred intensive research efforts to elucidate its pathogenesis, develop accurate diagnostic methods, and refine the treatment strategies. The significance of *H. pylori* lies not only in its prevalence, but also in its wide-ranging impact on human health. Additionally, *H. pylori* is recognized as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC); it is the only bacterium on the list with a strong association with gastric adenocarcinoma and is one of the leading causes of cancer-related deaths globally [7]. Furthermore, the bacterium's implications extend beyond the stomach, with the links to autoimmune disorders, cardiovascular diseases, and metabolic syndromes being explored. Understanding the pathogenesis, accurate diagnosis, and effective management of *H. pylori* infections are paramount in mitigating their impact on public health.

2. Pathogenesis of *Helicobacter pylori*

The pathogenesis of *H. pylori* may be studied at three distinct stages: the attachment to and colonization of the gastric mucosa, triggering and evading the immune responses of the host, and finally, the establishment of the disease [8].

2.1. Dispersal and Routes of Infection

H. pylori infections are often asymptomatic and usually acquired during childhood. However, around 30% of infected persons may show signs of gastrointestinal diseases, such as mild-to-severe cases of peptic ulcers, gastritis, and even gastric cancer and MALT lymphoma. *H. pylori* infections have a narrow host range, and therefore, the transmission routes usually include vertical and horizontal transmission. The former includes person-to-person transmission between genetically related individuals, while the latter includes persons exposed to infected people of a similar socioeconomic status [9]. While the exact route of transmission remains unclear, the four major routes of *H. pylori* infection include the fecal–oral route, the oral–oral route, the gastric–oral route, and gastro-gastric route which may occur through the ingestion of contaminated food, water or during endoscopic procedures [10].

2.2. Molecular Mechanisms of Infection

2.2.1. Attachment and Colonization

The molecular mechanisms orchestrating *H. pylori* infections are sophisticated processes crucial for the bacterium's successful establishment in the gastric mucosa. At the forefront of infection initiation is *H. pylori*'s adhesion and colonization strategies. The colonization of the pathogen is initiated first by the chemotaxis of the bacterial cells to the target site, which is mediated by the presence of certain receptors present on the host cells, mainly belonging to the Tlp family [11]. These receptors are known to be triggered by the presence of chemical signals, including urea, lactic acid, ROS species, and gastric juice, facilitating chemotactic responses to the gastric epithelium [11]. Flagellar motility allows *H. pylori* to navigate through the mucous layer and reach the gastric epithelium, contributing to its ability to firmly adhere to and colonize the mucosa [12]. Additionally, *H. pylori* can form biofilms, structured bacterial communities embedded in an extracellular matrix, enhancing adherence and providing protection against the host defenses and treatment therapies [13]. Furthermore, the bacterial outer membrane proteins, aka the surface adhesins, including BabA, SabA, AlpA/B, and OipA, enable the bacteria to adhere to gastric epithelial cells, paving the way for its persistence within the stomach [14].

2.2.2. Production of Virulence Factors

Various virulence factors, including those involved in motility, adhesion, urease and cytotoxin production, are essential for the pathogenesis of this bacterium [15].

2.2.3. CagA and VacA

Upon attachment, *H. pylori* engages in intricate host interactions, deploying an arsenal of virulence factors that manipulate host cell signaling. Among these, the CagA (cytotoxin-associated gene A) pathogenicity island is the main orchestrator [16]. Injected into the host cells via a type IV secretion system (T4SS), CagA triggers a cascade of events, disrupting cellular functions and contributing to the development of gastric pathologies [17]. CagA undergoes tyrosine phosphorylation, leading to the activation of various cellular signaling pathways [18]. This includes the aberrant activation of the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) pathways [19][20]. The dysregulation of these pathways contributes to cellular morphological changes, the disruption of cell polarity, and the initiation of oncogenic processes. This molecular hijacking of host cell signaling is a hallmark of *H. pylori*-induced pathogenesis [21]. The vacuolating toxin, VacA, is another key virulence factor, that exhibits multifaceted effects on the host cells [22]. As the name suggests, VacA disrupts the integrity of the gastric epithelial barrier by forming channels or pores in the cell membrane, leading to increased permeability [15]. Within the host cells, VacA modulates the apoptotic pathways, leading to both pro- and antiapoptotic effects depending on the cell type and environmental conditions. Furthermore, VacA toxin contributes to the formation of vacuoles within the host cells, impacting the cellular structure and function [23]. This toxin also interferes with and evades the immune responses by affecting the function of T cells and other immune cells. The consequences of these molecular interactions extend to the host's immune response [24][25]. *H. pylori* induces a chronic inflammatory state marked by the release of multiple pro-inflammatory cytokines, such as IL-8, IL-1α. IL-1β, and TNF α, among others, and the recruitment of immune cells to the gastric mucosa [26]. This inflammatory milieu is closely associated with the development of peptic ulcers, as the delicate balance between the protective mucosal mechanisms and bacterial aggression is disrupted [27]. The CagA and VacA proteins work together to induce *H. pylori*-associated gastric cancer. A study conducted by Abdullah et al. (2019) showed the functional interplay between the two oncoproteins, whereby the absence of VacA aids the host's system is able to degrade CagA, thereby preventing the accumulation of CagA in the gastric epithelial cells [28]. Importantly, the long-term consequences of *H. pylori* infection include an increased risk of developing gastric cancer. Chronic inflammation, coupled with the release of genotoxins and the induction of genetic instability, creates an environment conducive to oncogenesis and other gastric malignancies [29]. The interplay between *H. pylori's* virulence factors, such as CagA, VacA, and OipA, host genetic susceptibility, and environmental factors contribute to the complexity of this association [30]. Understanding these intricate molecular mechanisms is paramount for developing targeted therapeutic approaches and preventive strategies against *H. pylori* infections. The advances in elucidating these processes provide critical insights into the pathogenesis of *H. pylori*-related diseases and inform the development of novel interventions to mitigate the associated health risks.

2.2.4. Urease Production and Survival at Low pH

Urease is one of the more abundantly produced proteins expressed by the pathogen, accounting for almost 15% of the total proteins of the bacterium [31]. The production of urease is a characteristic feature of *H. pylori* and is widely used in the diagnosis of the infection as well [32]. Several studies in this regard have proved the role of urease in enabling the survival of the bacterium in the extremely low-pH acidic environment of the stomach by breaking down the urea into ammonia and carbon dioxide, thereby forming a pH-neutral environment around the bacterial cells (**Figure 1**). The other enzymes, including carbonic anhydrase, arginase, glutamine synthase, glutamate

dehydrogenase, and glutaminase, are also involved in the urease-dependent mechanism of survival under acidic conditions [33]. The hydrolysis of urea into ammonia also provides the pathogen with a steady source of nitrogen [34][35]. Survival at low pH is further supported by other urease-independent physiological factors, including the flagellar motility across the gastric mucus layer, which facilitates the movement of the bacterial cells in low-pH-level conditions [36]. Furthermore, DNA repair proteins, such as RecA, RecN, RecO, Hup, etc., are actively involved in repairing the DNA that may be damaged after being subjected to acid stress in the stomach [37][38]. *H. pylori* also exhibits chemotactic activity towards certain chemoattractants, such as carbonates and urea, which attract the bacterial cells towards the regions of higher pH in the gastric lining. Among the chemoreceptors of *H. pylori*, the Tlp family is crucial for the desirable chemotactic activity that promotes survival in an acid stress environment [39].

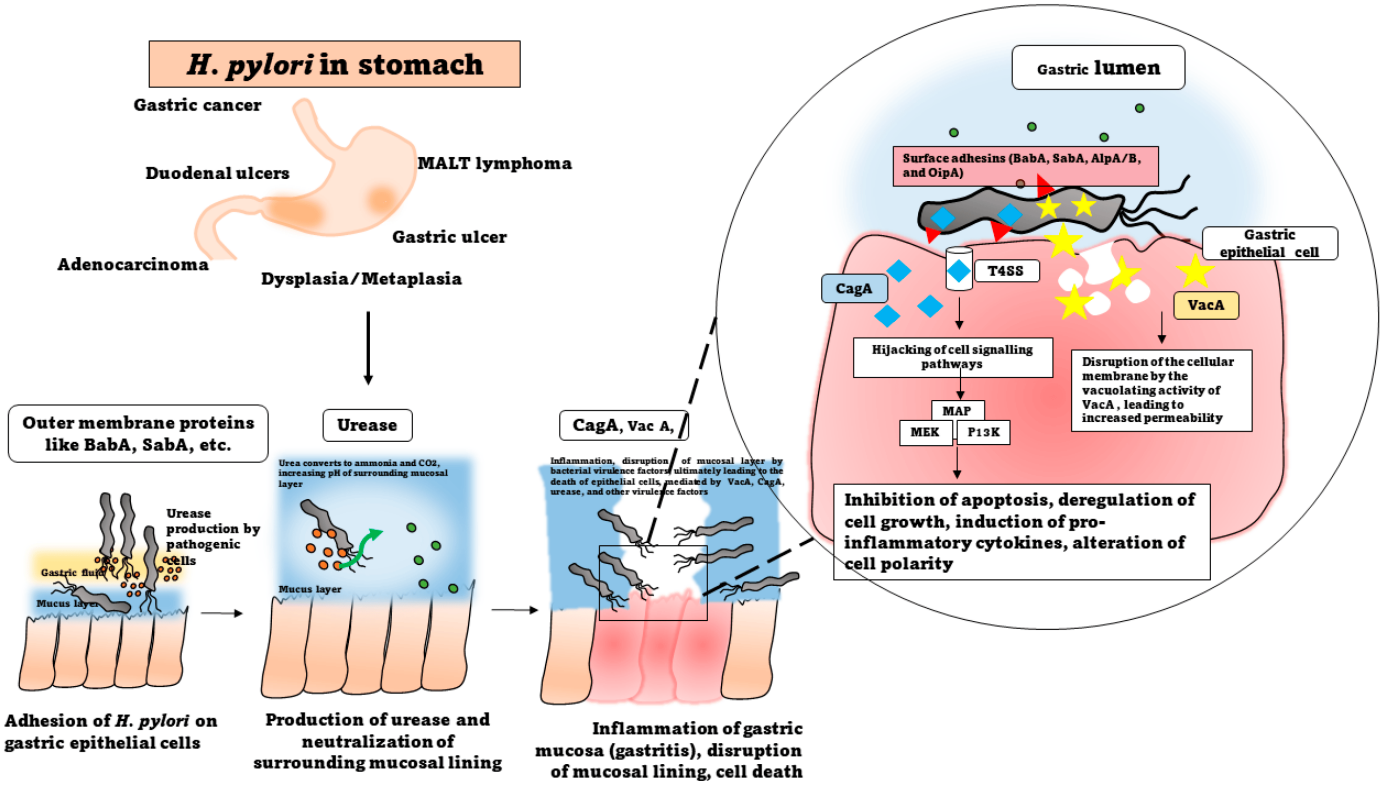

Figure 1. Pathogenesis of *H. pylori.*

2.3. Immune System Modulation and Induction of Inflammatory Responses

The immune response to *H. pylori* infection is a dynamic interplay between the bacterial factors and the host's immune system [40]. The pathogenesis of *H. pylori* infections unfold through a complex and multifaceted localized gastric inflammatory response [41]. In the innate immune phase, *H. pylori* induces a chronic inflammatory response in the gastric mucosa, mediated by the lipopolysaccharides and the peptidoglycan of the cell wall, and characterized by the release of neutrophils, macrophages, lymphocytes, and pro-inflammatory cytokines (such as interleukin-1β, interleukin-6, and tumor necrosis factor-α) and the recruitment of immune cells [42][43]. Innate immune activation spurred by bacterial components, like lipopolysaccharide and peptidoglycan, further amplifies the inflammatory cascade through pattern recognition receptors such as Toll-like receptors [44]. This sets the stage

for the adaptive immune response, where the CD4+ T-helper cells play a crucial role, particularly in promoting a Th1 response characterized by interferon-gamma secretion. Regulatory T cells are recruited, contributing to immune suppression, while the B cells produce antibodies against *H. pylori* [45][46]. However, the bacterium employs immune evasion strategies, such as urease production, antigenic variation, inhibition of recognition by PRRs, and molecular mimicry, to subvert recognition and signaling by the T and B cells [47]). The sustained presence of *H. pylori* leads to chronic inflammation, causing ongoing tissue damage and remodeling. The gastric epithelial cells undergo changes in turnover, with increased proliferation contributing to mucosal damage and ulcer formation [48]. Concurrently, disruptions in the tight junctions compromise the mucosal barrier integrity, facilitating *H. pylori* infiltration into the deeper mucosal layers [49]. The sustained release of inflammatory mediators, coupled with the induction of genetic instability, creates an environment conducive to oncogenesis [50]. This sustained inflammation is a central component of *H. pylori*-associated diseases and is implicated in the development of peptic ulcers and gastric cancer [2]. However, in the neighboring non-infected gastric cells, an adaptive immune response is triggered which prompts increased survival and proliferation, ultimately leading to the development of precancerous lesions in the gastric epithelium [51].

2.4. Modulation of Mucin Production

H. pylori influences mucin production in the gastric mucosa, impacting the protective mucous layer. The carbohydrate component of the mucins act as ligands that enable the binding of the bacterium to the gastric mucosal lining [52]. The bacterium can alter the expression of mucin genes and interact with mucins, like MUC5A and MUC1, directly, resulting in inhibition or the impairment of mucin turnover [53]. The changes in mucin production influence the composition of the mucosal glycocalyx, affecting the adherence and colonization of *H. pylori*. Moreover, this modulation of mucin production contributes to the bacterium's ability to evade the host defenses and establish persistent infections [54]. Unraveling the nuances of immune system modulation in *H. pylori* infection is paramount for devising effective therapeutic interventions and preventive strategies in the ongoing pursuit of managing the associated diseases. The ongoing research continues to unveil the complexities of this host–pathogen interaction.

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