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Review article

The Interplay of Helicobacter pylori Virulence Factors and Host Immune Responses: Implications for Disease Management

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Abstract

Helicobacter pylori (H. pylori), which was first discovered in 1982 and is found all over the world, has been linked to gastritis, gastric ulcers, and duodenal ulcers. The prevalence of H. pylori infection exhibits significant global variation. This review meticulously explores the pathogenesis of *H. pylori* infection, unravelling the bacterium's strategies, including adherence to the gastric epithelium, mucosal colonization, disruption of intercellular junctions, and evasion of host immune defences. Virulence factors such as urease, phospholipases, adhesins, and the Cag pathogenicity island are scrutinized for their pivotal roles. It is looked at how the bacteria can colonize the stomach lining with the help of a group of unipolar flagella and how well they can break down mucin and affect the protection of the local lining. Virulence factors like urease, phospholipases, and adhesins are studied to see what role they play in infection. The *Cag* pathogenicity island *(CagPAI)* causes inflammation by releasing interleukin-8, which can lead to chronic gastritis, peptic ulcers, and a higher risk of gastric cancer. Host factors, encompassing immune responses and genetic polymorphisms, are explored for their influence on clinical outcomes. Notably, environmental factors like low socio-economic status, poor sanitation, and inadequate water supply contribute to *H. pylori* prevalence. Antioxidants, particularly vitamin C, are identified as protective, while tobacco smoking emerges as an additional etiological factor. In conclusion,this comprehensive analysis consolidates the most recent advancements in the examination of *H. pylori* virulence determinants, with a specific emphasis on their interactions with host responses and environmental variables. The insights provided are pivotal for advancing therapeutic strategies, to mitigate the global health impact of *H. pylori*-related diseases.

Keywords: Helicobacter pylori; Vaculating Cytotoxin A (VacA); Cag Pathogenicity Island, Host immune response

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1. Introduction

Helicobacter pylori, a Gram-negative bacterium characterized by its spiral shape with and a genome of around 1.65 Mb, that affects approximately 50% of the global human population. The cultivation of this bacteria was first conducted in 1982, leading to the later discovery of its role as the etiological factor in gastritis, as well as gastric and duodenal ulcers.[1] The prevalence of *Helicobacter pylori (H. pylori)* infection exhibits significant variationacross worldwide. Notably, Latin American have a high prevalence range of 75 to 83% whereas Japan and the United States exhibit comparatively

lower prevalence rates of 39.6% and 17.1%, respectively.[2] There is a well-established correlation between *Helicobacter pylori* infection and several gastrointestinal disorders, such as gastritis, peptic ulcer, duodenal ulcer, and gastric cancer. The complicated interaction between bacterial, host, and environmental variables mediates various illness and its consequences. The elucidation of the precise contribution of bacterial virulence factors to the pathogenesis of *Helicobacter pylori* will greatly enhance the development of vaccines and other therapeutic approaches.[3] This review is designed to clarify current advancements in the understanding of Helicobacter pylori virulence factors and their role in the etiology of related diseases.

2. Pathogenesis of *H. pylori infection*

H. pylori exhibits its pathogenic traits by (i) adhering to the gastric epithelium; (ii) colonizing the mucous gel layer, thereby enhancing permeability to hydrogen ions and pepsin; (iii) infiltrating and disrupting intercellular junctions; (iv) invading gastric glands and canaliculi of parietal cells; (v) evading the host's immune defenses; and (vi) releasing enzymes and generating cytotoxins.[4]

2.1 Colonization of the gastric mucosa

H. pylori usually colonizeas commensal in the stomach.[5] The mucosal barrier lining the stomach protects it from the harmful effects of gastric secretions and other substances, protecting the stomach's epithelial and it's deeper layers.[6] Tight cellular junction and the presence of a protective mucus layer preserve the integrity of the mucosal layer. Prostaglandin is a chemical messenger that protects the stomach lining by promoting mucus production, enhancing bicarbonate secretion, and improving blood flow.[7] *H. pylori* is an infectious agent that usually adheres only to the mucus-secreting cells of the stomach (except in Barrett's oesophagus and duodenal ulcers, where gastric mucosa replaces the epithelial layer), thrives in the acid environment of the stomach, and disrupts the mucosal barrier.[5,8] Motility of *H.pylori* within the gastric mucosa is aided by a bundle of unipolar flagella that possess a sheath to prevent depolymerization in an acidic environment. The organism remains mainly in the mucus, while a subpopulation adheres to specific receptors of gastric epithelial cells.[5,9] *H. pylori* degrades mucin and has the capacity to interfere with the local protection of the mucosa against gastric acid. It also may produce toxins that directly damage the mucosa and produce ulceration in other ways.[10] *H. pylori* has evolved several mechanisms to evade primary host defenses such as acidity and peristalsis causes persistent infection within the stomach.[11] This organism elaborates a number of enzymes such as urease, catalase, oxidase, hydrogenase etc. Catalase helps the organism to survive in the host by preventing the formation of oxygen metabolites from hydrogen peroxide in neutrophils.[8,12]

2.2 Virulence factors

a) Urease

Urease is an important virulence factor for *H. pylori* which metabolizes urea producing ammonia. Thus, the pathogen can successfully survive in the gastric lumen (pH 1-2) for a short period time and it penetrates into the mucus layer of stomach with bicarbonate-buffered, its real habitat.[5] This enzyme may assimilate organic nitrogen due to its cytoplasmatic urease activity. Ammonia may affect stomach mucosa and epithelial permeability. Urease also activates mononuclear phagocytes and produces inflammatory cytokines.[13,14]

b) Phospholipases

H. pylori phospholipases induce generation of productssuch as lysolecithin which disrupt the protective phospholipid rich layer on the apical membrane of mucus cells.[13]

c) Neutrophil activating protein

*H. pylor*i activate neutrophils and increase their adhesion to endothelial cells by expressing a 150 kDa activating protein (Hp-Nap) with 10 identical subunits from the *napA* gene.The purified protein activates neutrophils dose-dependently to produce oxygen free radicals and attach to endothelium cells, becoming Hp-Nap pathogenic. Additional information is required before Hp-Nap is considered an important bacterial virulence component.[15]

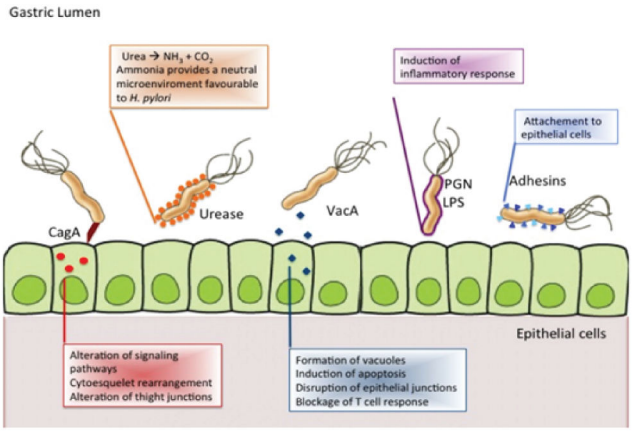

Figure 1: Virulence factors of *H. pylori*[16]

d) Adhesins

*H. pylor*i adheres to stomach epithelial receptors using adhesins. Several specific receptors are also involved including lipids, gangliosides and sulfated carbohydrates, and other different types of adhesins such as SabA, OlpA, A1pA, and A1pB, including the BabA2; outer membrane protein, which is encoded by the bab (blood group antigen binding) genes[17,18]

e) IceA (induced by contact with epithelium)

The gene encoding *IceA* has been identified in isolates from patients with peptic ulcer, independently of the *vacA* and *cagA* genotype.[19] The expression *ofIceA* is induced by adherence of *H. pylori* to gastric epithelium. DNA sequencing has revealed the presence of two families: *IceA*1 and *IceA*2. Strains with the *IceA1* gene are most frequently associated with peptic ulceration and increase the production of IL-8 .[20]

f) Vaculating Cytotoxin A (VacA)

VacA is an oligomeric toxin with 87 kDa active subunits from low pH treatment. Antiserum against these proteins neutralizes the protein's cytotoxicity. It causes vacuolar degeneration of target cells by interfering with intracellular membrane fusion.[21] The vacuolation mechanism involves the stimulation of adenosine tri phosphate dependent proton pump and of a small GTPase. vacA induces an mitochondrial damage, leading to impairment of the gastric epithelial cells cycle.[22] Mosaicism in vacA alleles is expressed by vacA subtypes of which three concern signal sequence regions *(s1a, s1b and s2)* and two middle region motifs *(m1 and m2)*.[23,24] The s1a strains produce higher levels of cytotoxin with more severe gastric inflammation and duodenal ulceration than the other two allelic sub types. The *m1* middle region allele is more frequently associated with a higher level of gastric damage as compared with the *m2* form. Virulence may be assessed by vacuolating cytotoxin activity, *VacA* serology, and genotyping. A non-invasive test like *vacA* serology would be better, *vacA* signal sequence type better indicates peptic ulceration. Infection with *vacA sla* strains causes peptic ulceration more than *sib* strains. For determination of *vacA* genotyping requires stomach biopsy, that's why *vacA* genotyping cannot be used in non-invasive screening strategies. It is currently regarded as a best research tool.[25]

g) Cag Pathogenicity Island

Helicobacter pylori *(H. pylori)* strains from gastric epithelium are classified as type I and type II. Type I is associated with severe diseases due to a specific genomic locus, the *Cag* pathogenicity island *(CagPAI)*, inducing inflammation.[26,27] The *CagPAI*, containing 31 genes, triggers the release of inflammatory chemokine (IL-8), leading to neutrophil infiltration. Type I strains, with the *CagPAI*, are linked to chronic gastritis, peptic ulcers, and an increased risk of gastric cancer.[25,28] The *Cag*A gene, located in *CagPAI*, encodes a 120 kDa immunodominant antigen associated with cytotoxin expression. *Cag*A-positive *H. pylori* infections have been linked to food allergies. The presence of both *Cag*-positive and *Cag*-negative strains in a patient suggests a dynamic balance affecting disease expression.[4] *Cag*A serology, indicating *Cag*A presence, is a useful virulence marker. However, treating only *Cag*A-positive individuals may lead to unnecessary treatment, considering the common occurrence of CagA-positive strains. Treating all *H. pylori* infections could be an alternative, but it poses challenges like expense, side effects, and antibiotic resistance concerns.[25]

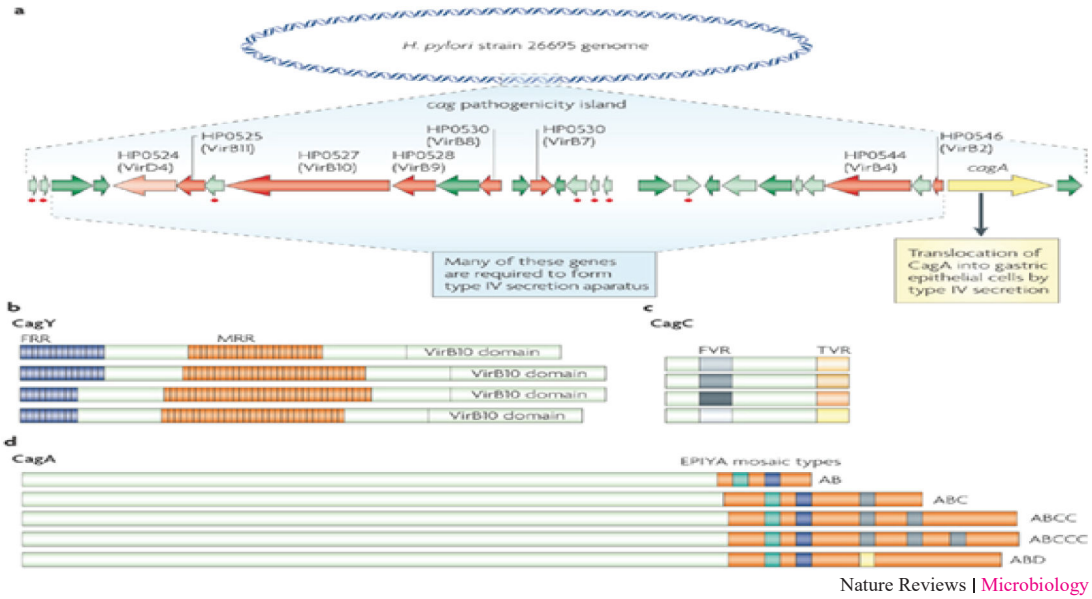

Figure 2:Arrangement of cag PAI genes in *H. pylori* strain 26695[29]

[Most of the cag genes may be involved in the type IV secretion pathway that transports cagA into gastric epithelial cell cytoplasm. Seven red genes resemble type IV secretion system components. The island encodes proteins that induce gastric epithelial cells to produce IL-8 and translocate *cagA* from the bacteria to host cells. All genes with arrows in dark red and green are necessary for IL-8 induction, whereas those with lighter colors are not. The non-marked genes are important for *cagA* translocation, but the red-dotted arrows are not. b–d]

h) Direct neutrophil activation by H. pylori

H. pylori not only trigger the production of the cytokine IL-8 in epithelial cells but also directly activate neutrophils. There are two types of *H. pylori* based on the strength of this activation. Approximately 50% of strains induce a quick and robust oxidative burst in neutrophils more prevalent in patients with peptic ulcer, while the remaining 50% induce a slower and weaker burst.[30]

i) Duodenal ulcer promoting gene (dupA)

Duodenal Ulcer Promoting Gene (*dup*A) in the *H. pylori* genome's plasticity zone may indicate virulence marker. Lu et al. (2005)[31]found that *dup*A-positive strains increased duodenal ulcer risk and decreased stomach cancer risk in Colombia, South Korea, and Japan. Later studies in Belgium, South Africa, China, and the US revealed no relationship between *dup*A expression and duodenal ulcers but did uncover a link to stomach cancer.[32] Japanese and Swedish strains had no association between *dup*A expression and stomach cancer or duodenal ulcers, but Chinese strains did.[33] *dup*A may cause duodenal ulceration and stomach cancer in some people but not all.

2.3 Host factors responsible for *H. pylori* infection

Host-related factors play a crucial role in determining the clinical outcome of *H. pylori* infections, particularly those influencing the growth of the bacterium in the stomach. One significant factor is the variation in gastric acid production among individuals, which can impact the growth and localization of *H. pylori* in the stomach mucosa, as well as influence the growth of metaplastic gastric tissue in the duodenum, which provides additional niche for *H. pylori*. Additionally, polymorphisms in the receptors on gastric epithelial cells to which *H. pylori* adheres, or variations in the composition of gastric mucous, may also be key determinants. Gender is another factor, with *H. pylori* infection being more prevalent in men aged 20 to 39 years compared to women, suggesting a gender-specific influence on infection rates.[34,35]

a) Host immune response

The immune response to *H. pylori* is crucial due to concerns about potential damage to host tissues from leukocyte products. Additionally, there is interest in exploring immunization possibilities against *H. pylori.* The ideal host response should effectively clear the infection without causing excessive inflammation. However, evidence, including studies by Suarez et al. (2006)[36] and Tanih et al. (2010)[37], indicates that the immune response may contribute to *H. pylori* pathogenesis. Instead of eliminating the bacteria, the immune response can lead to the destruction of epithelial cells and thinning of the mucosal lining, increasing mucosal contact with luminal acid.[38,39]

b) Innate immune response to *H. pylori*

The immune-pathogenesis of *H. pylori* involves the up-regulation of various genes associated with the innate immune system, including Toll-like receptors (TLRs), complement factor C3, lactoferrin, and bactericidal/ permeability-increasing protein.[9] TLRs, particularly TLR4, play a crucial role in recognizing bacterial antigenic molecules and are expressed by various cell types in the gastrointestinal tract. Activation of TLRs, often through bacterial lipopolysaccharide (LPS) signaling pathways, leads to NF-KB activation and the expression of pro-inflammatory genes. This process is evident in antigen-presenting cells like monocytes and dendritic cells. Contact with *H. pylori* induces the secretion of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-8, which act as local chemo-attractants and promoting granulocytic infiltration.[39]

c) Adaptive immunity

i) Cellular immune response

After innate immune responses failed to remove *H. pylori,* adaptive immune responses evolved. Polymorph nuclear leukocytes (PMN), T lymphocytes, macrophages, and plasma cells infiltrate the stomach during *H. pylori* inflammation. *Helicobacter pylori* attaches to stomach mucosal cells and releases chemicals that change their function.[40,41] Chronic active gastritis increases the CD4/CD8 T-cell ratio and accumulates CD4+ T-helper cells in the lamina propia.[42] Numerous studies reveal a polarized T helper cell response to *H. pylori,* with CD4+ T cells in infected patients producing Th1 cytokines (lL-12, IFN-γ, and TNF) but not Th2 cytokines (IL-4).[43,44] Gastric epithelium and activated macrophages generate cytokines, especially IL-8. While presenting *H. pylori* antigens to particular T cells in the gastric antrurn, antigen presentation cells also produce cytokines such IL-I, lL-6, TNF-α, and IL-12, which significantly impact the developing T-cell response.[43] Th17 CD4+ T cells, which cause infections and inflammation, also invade the stomach mucosa. Th17 are generated in gastric stroma during *H. pylori* infection and gastric cancer, suggesting an association between inflammation and carcinogenesis.[45]

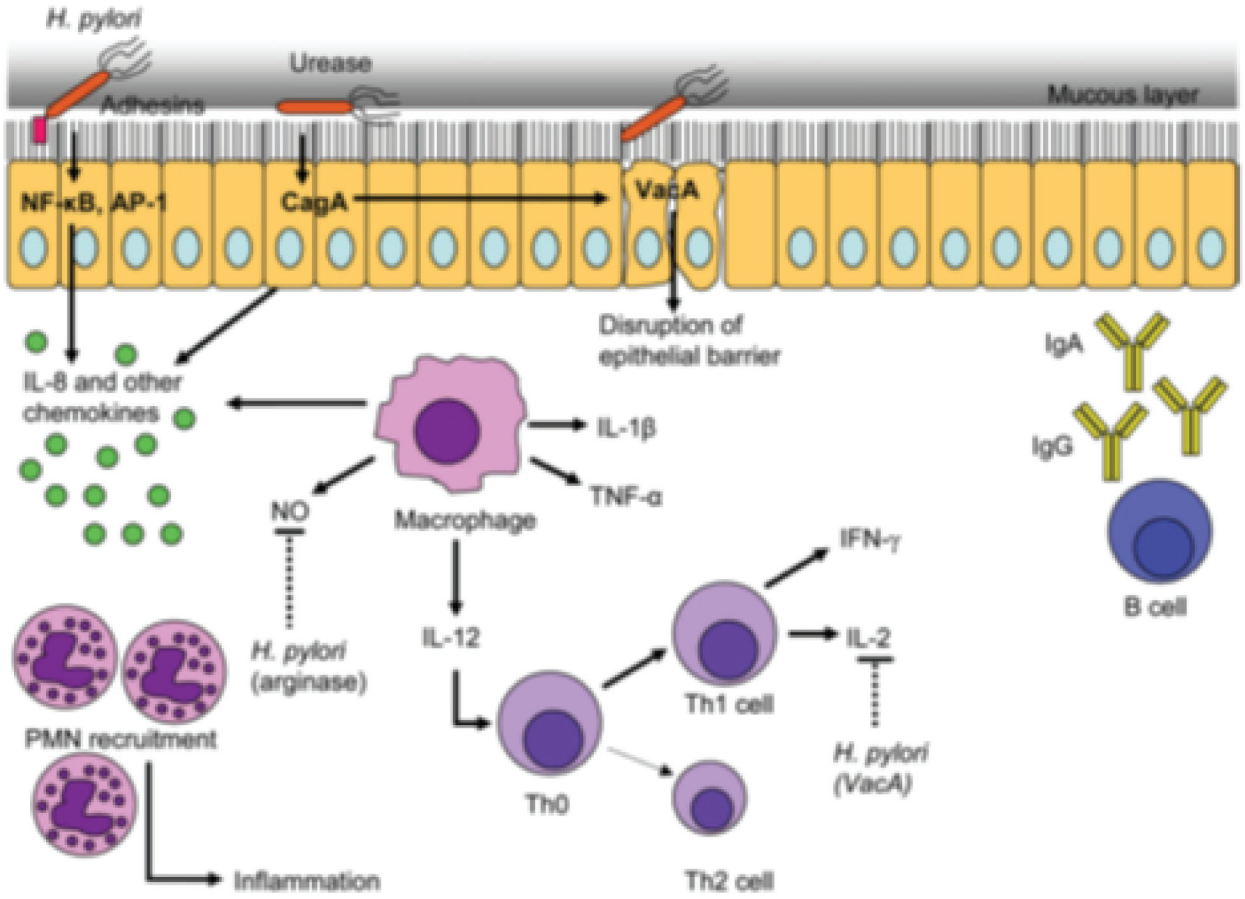

Figure 3: *H. pylori* pathogenesis, the inflammatory immune response and some of escape mechanisms[46]

During *H. pylori* infection gastric B cells detected which are often auto-reactive that indicate it leads to the development of gastric autoimmunity.In uncomplicated chronic gastritis and gastric MALTomas most of gastric *H. pylori*-specific T cells showed combined secretion of both Th1- and Th2-type cytokines.[47]

Some infection with *H. pylori* elicits Th2 instead of Th1 immune responses, which could possibly change the *H.pylori*-induced protective immune response to the gastric mucosa.Reports have indicated that Th2 response may provide protection against gastric cancer.[46]

ii) Humoral response

In response to H. pylori infection, individuals develop a robust antibody response. Both systemic and local antibodies are produced, including IgA and IgG. IgA, produced by plasma cells in the gastric mucosa, plays a crucial role in neutralizing urease and *VacA*, inhibiting *H. pylori* adherence to the gastric mucosa.[48–50] IgG antibodies enhance phagocytosis of *H. pylori,* and their binding triggers complement activation through classical or alternative pathways. This multifaceted antibody response is vital in the immune defense against *H. pylori* infection.[51]

iii) Role of host cytokine gene polymorphism in H. pylori induced gastric pathology

Host genetic factors, particularly cytokine gene polymorphisms, play a significant role in the pathology of gastro-duodenal diseases. These polymorphisms can affect the secretion of cytokines, influencing the magnitude of the immune response and contributing to individual clinical outcomes. The interaction between *H. pylori* and host cells induces genetic alterations, promoting gastric carcinoma development.[52]

Deoxyribonucleic acid (DNA) sequences of the human genome reveal that many genes are polymorphic. In the coding or non-coding regions of specific genes, there may be either a single base pair substitution or a variable number of tandem repeats (VNTR) of a short repetitive DNA sequence. These variations or polymorphisms may influence the rate of gene transcription, the stability of the messenger ribonucleic acid (mRNA) or the quantity and activity of the resulting protein. Thus, the susceptibility or

severities of a number of disorders are influenced by possession of specific alleles of polymorphic genes.[53]
Cytokine gene polymorphisms have recently attracted considerable interest since it has been discovered that different alleles of cytokine genes are associated with different immunomodulatory diseases. It directly influence interindividual variation in the magnitude of cytokine response, and this clearly contributes to an individual's ultimate clinical outcome.[54] Genes encoding cytokines and related molecules harbor polymorphic regions, which are considered to alter gene transcription and thereby influence inflammatory processes in response to infectious disease.[53]

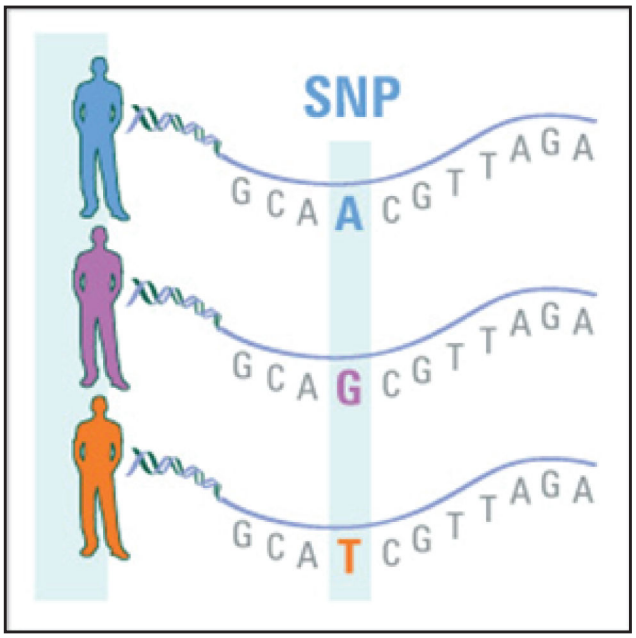

Figure 4: Single Nucleotide polymorphism

In several circumstances, chemokines may indicate blood cell migration. The main mediators of granulocyte accumulation are C-X-C chemokines. In *H. pylori*-associated gastritis stomach biopsy samples, the chemokine interleukin-8 (IL-8) is increased.[55] IL-8 has a key function in *H. pylori*-induced diseases. Neutrophils and lymphocytes are strongly attracted by it. It affects cell proliferation, migration, and tumor angiogenesis.[56] Transepithelial signal transmission is thought to initiate the inflammatory response in *H. pylori*-associated gastritis since the bacterium is noninvasive. Chemokines may induce second signals when bacteria are attached to the epithelium, among the various cytokines that may be generated by bacterial infection and cause pathologic alterations in inflammation. Thus, it is not unexpected that multiple studies have identified IL-8 as a key modulator of *H. pylori*-associated gastritis..[57,58] High IL-8 levels are related to *H. pylori*-associated gastritis. A particular IL-8 gene polymorphism (-251 T/A) increases IL-8 production, severe inflammation, and precancerous stomach anomalies. The polymorphism is associated to *H. pylori*, peptic ulcer disease, and chronic gastritis. Some studies relate IL-8 polymorphisms to stomach cancer susceptibility, but outcomes vary by demographic and geography. In conclusion, host genetic variables, notably cytokine gene polymorphisms, aggravate *H. pylori* infection and gastroduodenal disorders.[59]

2.5.4 Environmental factors

Low-income people with poor sanitation, congested living circumstances, and limited water supply often have *H. pylori* infection. An essential antioxidant, ascorbic acid scavenges reactive oxygen species and suppresses N nitrosation. Infection incidence decreases with antioxidant micronutrient consumption, especially vitamin C.Consuming more fruits and vegetables reduces duodenal ulcer risk. Smoking and having a family history increase the incidence of peptic ulcers, especially in males.[60] Low-income nations with unhygienic lifestyle had greater sero-conversion rates and higher reinfection rates following *H. pylori* eradication.[61]

Conclusion

Helicobacter pylori, a globally prevalent Gram-negative bacterium, plays a pivotal role in various gastrointestinal disorders. This review provides the pathogenesis of *H. pylori* infection, emphasizing the significance of virulence factors, host immune responses, and environmental factors. The interplay of bacterial adherence, colonization, immune activation, and genetic polymorphisms underscores the complexity of disease outcomes. Understanding these multifaceted interactions is crucial for advancing therapeutic strategies, including vaccine development, to mitigate the impact of *H.pylori*-related diseases globally.

References

1. Boneca IG, Reuse H de, Epinat J-C, et al. A revised annotation and comparative analysis of Helicobacter pylori genomes. Nucleic Acids Res 2003; 31(6): 1704–1714.

2. Calvet X, Ramírez Lázaro M-J, Lehours P, et al. Diagnosis and Epidemiology of Helicobacter pylori Infection. Helicobacter 2013; 18 (1): 5–11.

3. Kao C-Y, Sheu B-S, Wu J-J. Helicobacter pylori infection: An overview of bacterial virulence factors and pathogenesis. Biomed J 2016; 39: 14–23.

4. Donelli LC Gianfranco. Virulence Factors of Helicobacter pylori. Microbial Ecology in Health and Disease 2000; 12(2): 259–262.

5. Kusters JG, van Vliet AHM, Kuipers EJ. Pathogenesis of Helicobacter pylori Infection - PMC. 2006; 19(3): 449–490.

6. Clamp JR, Ene D. The gastric mucosal barrier. Methods Find Exp Clin Pharmacol 1989; 11 Suppl 1: 19–25.

7. Laine L, Takeuchi K, Tarnawski A. Gastric Mucosal Defense and Cytoprotection: Bench to Bedside. Gastroenterology 2008; 135 (1): 41–60.

8. Figueiredo C, Machado JC, Yamaoka Y. Pathogenesis of Helicobacter pylori Infection. Helicobacter 2005; 10 Suppl 1: 14–20.

9. Peek RM. Pathogenesis of Helicobacter pylori infection. Springer Semin Immunopathol 2005; 27: 197–215.

10. Blaser MJ, Berg DE. Helicobacter pylori genetic diversity and risk of human disease. J Clin Invest 2001; 107(7): 767–773.

11. Ernst PB, Peura DA, Crowe SE. The translation of Helicobacter pylori basic research to patient care. Gastroenterology 2006; 130 (1): 188–206; quiz 212–213.

12. Radosz-Komoniewska H, Bek T, Jóźwiak J, et al. Pathogenicity of Helicobacter pylori infection. Clinical Microbiology and Infection 2005; 11(8): 602–610.

13. Mauch F, Bode G, Ditschuneit H, et al. Demonstration of a phospholipid-rich zone in the human gastric epithelium damaged by Helicobacter pylori - PubMed. 1993; 105(6): 1698–704.

14. Phadnis S, Parlow M, Levy M, et al. Surface localization of Helicobacter pylori urease and a heat shock protein homolog requires bacterial autolysis. - PMC. 1996; 64 (3): 905–12.

15. Evans DJ, Evans DG, Takemura T, et al. Characterization of a Helicobacter pylori neutrophil- activating protein. Infect Immun 1995 (6); 63: 2213–2220.

16. Stephanie E, E M-V, G R, et al. The Role of CagA Protein Signaling in Gastric Carcinogenesis — CagA Signaling in Gastric Carcinogenesis | IntechOpen, https://www.intechopen.com/chapters 11/41562 (accessed 28 November 2023).

17. Simon PM, Goode PL, Mobasseri A, et al. Inhibition of Helicobacter pylori binding to gastrointestinal epithelial cells by sialic acid-containing oligosaccharides. Infect Immun 1997; 65 (2): 750–757.

18. Maeda S, Mentis AF. Pathogenesis of Helicobacter pylori Infection. Helicobacter 2007; 12 (s1): 10–14.

19. Peek RM, Thompson SA, Donahue JP, et al. Adherence to gastric epithelial cells induces expression of a Helicobacter pylori gene, iceA, that is associated with clinical outcome. Proc Assoc Am Physicians 1998; 110(6): 531–544.

20. Peek RM, Miller GG, Tham KT, et al. Heightened inflammatory response and cytokine expression in vivo to cagA+ Helicobacter pylori strains. Lab Invest 1995; 73 (6): 760–770.

21. Cover TL, Halter SA, Blaser MJ. Characterization of HeLa cell vacuoles induced by Helicobacter pylori broth culture supernatant. Hum Pathol 1992(9); 23: 1004–1010.

22. Papini E, Satin B, Norais N, et al. Selective increase of the permeability of polarized epithelial cell monolayers by Helicobacter pylori vacuolating toxin. J Clin Invest 1998; 102(4): 813–820.

23. Perez-Perez GI, Peek RM, Atherton JC, et al. Detection of anti-VacA antibody responses in serum and gastric juice samples using type s1/m1 and s2/m2 Helicobacter pylori VacA antigens. Clin Diagn Lab Immunol 1999; 6(4): 489–493.

24. Ge Z, Taylor DE. Helicobacter pylori--molecular genetics and diagnostic typing. Br Med Bull 1998; 54(1): 31–38.

25. Atherton JC, Peek RM, Tham KT, et al. Clinical and pathological importance of heterogeneity in vacA, the vacuolating cytotoxin gene of Helicobacter pylori. Gastroenterology 1997; 112(1): 92–99.

26. Tomb JF, White O, Kerlavage AR, et al. The complete genome sequence of the gastric pathogen Helicobacter pylori. Nature 1997; 388(6642): 539–547.

27. Covacci A, Telford JL, Del Giudice G, et al. Helicobacter pylori virulence and genetic geography. Science 1999; 284(5418): 1328–1333.

28. Baggiolini M, Dewald B, Moser B. Interleukin-8 and related chemotactic cytokines--CXC and CC chemokines. Adv Immunol 1994; 55: 97–179.

29. Suerbaum S, Josenhans C. Helicobacter pylori evolution and phenotypic diversification in a changing host. Nat Rev Microbiol 2007; 5(6): 441–452.

30. Rautelin H, Blomberg B, Järnerot G, et al. Nonopsonic activation of neutrophils and cytotoxin production by Helicobacter pylori: ulcerogenic markers. Scand J Gastroenterol 1994; 29(2): 128–132.

31. Lu H, Hsu P-I, Graham DY, et al. Duodenal ulcer promoting gene of Helicobacter pylori. Gastroenterology 2005; 128(4): 833–848.

32. Argent RH, Burette A, Miendje Deyi VY, et al. The presence of dupA in Helicobacter pylori is not significantly associated with duodenal ulceration in Belgium, South Africa, China, or North America. Clin Infect Dis 2007; 45(9): 1204–1206.

33. Schmidt H-MA, Andres S, Kaakoush NO, et al. The prevalence of the duodenal ulcer promoting gene (dupA) in Helicobacter pylori isolates varies by ethnic group and is not universally associated with disease development: a case-control

study. Gut Pathog 2009; 1(1): 5.

34. Borén T, Falk P, Roth KA, et al. Attachment of Helicobacter pylori to human gastric epithelium mediated by blood group antigens. Science 1993; 262(5141): 1892–1895.

35. Replogle ML, Glaser SL, Hiatt RA, et al. Biologic sex as a risk factor for Helicobacter pylori infection in healthy young adults. Am J Epidemiol 1995; 142(8): 856–863.

36. Suarez G, Reyes VE, Beswick EJ. Immune response to H. pylori. World J Gastroenterol 2006; 12(35): 5593–5598.

37. Tanih NF, McMillan M, Naidoo N, et al. Prevalence of Helicobacter pylori vacA, cagA and iceA genotypes in South African patients with upper gastrointestinal diseases. Acta Trop 2010; 116(1): 68–73.

38. Fan XJ, Chua A, Shahi CN, et al. Gastric T lymphocyte responses to Helicobacter pylori in patients with H pylori colonisation. Gut 1994; 35(10): 1379–1384.

39. Bodger K, Crabtree JE. Helicobacter pylori and gastric inflammation. Br Med Bull 1998; 54(1): 139–150.

40. Avilés-Jiménez F, Reyes-Leon A, Nieto-Patlán E, et al. In vivo expression of Helicobacter pylori virulence genes in patients with gastritis, ulcer, and gastric cancer. Infect Immun 2012; 80(2): 594–601.

41. Chatterjee S. H. pylori-induced Gastric Ulcer: Pathophysiology and Herbal Remedy,https://www.academia.edu/26696032/H_pylori_induced_Gastric_Ulcer_Pathophysiology_and_Herbal_Remedy (accessed 28 November 2023).

42. Tummala S, Keates S, Kelly CP. Update on the immunologic basis of Helicobacter pylori gastritis. Curr Opin Gastroenterol 2004; 20(6): 592–597.

43. Yamasaki R, Yokota K, Okada H, et al. Immune response in Helicobacter pylori-induced low-grade gastric-mucosa-associated lymphoid tissue (MALT) lymphoma. J Med Microbiol 2004; 53(1): 21–29.

44. Fritz EL, Slavik T, Delport W, et al. Incidence of Helicobacter felis and the effect of coinfection with Helicobacter pylori on the gastric mucosa in the African population. J Clin Microbiol 2006; 44(5): 1692–1696.

45. Pinchuk IV, Morris KT, Nofchissey RA, et al. Stromal cells induce Th17 during Helicobacter pylori infection and in the gastric tumor microenvironment. PLoS One 2013; 8: e53798.

46. Portal-Celhay C, Perez-Perez GI. Immune responses to Helicobacter pylori colonization: mechanisms and clinical outcomes. Clinical Science 2006; 110(3): 305–314.

47. Hasni S, Ippolito A, Illei G. Helicobacter pylori and autoimmune diseases. Oral Diseases 2011; 17(7): 621–627.

48. Nessa J, Chart H, Owen RJ, et al. Human serum antibody response to Helicobacter pylori whole cell antigen in an institutionalized Bangladeshi population. J Appl Microbiol 2001; 90(1): 68–72.

49. Tosi MF, Czinn SJ. Opsonic activity of specific human IgG against Helicobacter pylori. J Infect Dis 1990; 162(1): 156–162.

50. Mattsson A, Quiding-Järbrink M, Lönroth H, et al. Antibody-secreting cells in the stomachs of symptomatic and asymptomatic Helicobacter pylori-infected subjects. Infect Immun 1998; 66(6): 2705–2712.

51. Berstad AE, Høgåsen K, Bukholm G, et al. Complement activation directly induced by Helicobacter pylori. Gastroenterology 2001; 120(5): 1108–1116.

52. Rad R, Dossumbekova A, Neu B, et al. Cytokine gene polymorphisms influence mucosal cytokine expression, gastric inflammation, and host specific colonisation during Helicobacter pylori infection. Gut 2004; 53(8): 1082–1089.

53. Moorchung N, Srivastava AN, Gupta NK, et al. Cytokine gene polymorphisms and the pathology of chronic gastritis. Singapore Med J 2007; 48(5): 447–454.

54. Oluwasola AO. Genetic determinants and clinico-pathological outcomes of helicobacter pylori infection. Ann Ib Postgrad Med 2014; 12(1): 22–30.

55. Rieder G, Hatz RA, Moran AP, et al. Role of adherence in interleukin-8 induction in Helicobacter pylori-associated gastritis. Infect Immun 1997; 65(9): 3622–3630.

56. Yuan A, Chen JJW, Yao P-L, et al. The role of interleukin-8 in cancer cells and microenvironment interaction. Front Biosci 2005; 10: 853–865.

57. Taub DD, Oppenheim JJ. Review of the chemokine meeting the Third International Symposium of Chemotactic Cytokines. Cytokine 1993; 5(3): 175–179.

58. Whicher JT, Evans SW. Cytokines in disease. Clin Chem 1990; 36(7): 1269–1281.

59. Smith SI, Lück PC, Bayerdöffer E, et al. Genotyping of Nigerian Helicobacter pylori isolates by pulsed-field gel electrophoresis. J Med Microbiol 2003; 52(10): 931.

60. Ostensen H, Gudmundsen TE, Ostensen M, et al. Smoking, alcohol, coffee, and familial factors: any associations with peptic ulcer disease? A clinically and radiologically prospective study. Scand J Gastroenterol 1985; 20(10): 1227–1235.

61. Sobala GM, Schorah CJ, Sanderson M, et al. Ascorbic acid in the human stomach. Gastroenterology 1989; 97(2): 357–363.