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THE MOLECULAR BATTLE FIELD: HOST PATHOGEN INTERACTIONS IN H. PYLORI INDUCED GASTRIC DISEASE

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Abstract

Background:
Helicobacter pylori is a usual bacterium of the stomach that has been linked to chronic inflammation of the stomach lining, the formation of stomach ulcers, instability of the stomach's inner lining, and cancer of the stomach. Gastric diseases H. pylori cause cannot be attributed to the colonization of the bacterium alone.

Objective:
This thesis review aimed to analyze the existing literature on host–pathogen interactions in the context of H. pylori-induced gastric disease, with particular emphasis on bacterial virulence, host defense, molecular mechanisms, and disease development.

Methodology:
This research was executed via a systematic literature review. Pouring through articles that had been fully accessed and had completed peer review from a number of reliable databases: Scopus, Web of Science, PubMed, and Google Scholar. Throughout the process, 120 articles that had been published between the years of 1984 and 2025 were sourced, then further narrowed down to 75

Results:
The examined research explains that H. pylori affects the stomach tissue using a number of integrated techniques. Epithelial injury, inflammation, and malignant transformation, as well as altered autophagy and mitochondrial dysfunction, are caused by CagA, VacA, and the cag-T4SS complex. CagA, VacA, and the Cag-T4SS complex, among others, also assist in immunoactivation, inflation signal and dysbiosis of microbiota.

Conclusion:
This review found that Helicobacter pylori-initiated gastric ailments are poly-descriptive diseases that entail endless reciprocal relationships of the microbial virulence and host molecular mechanisms. In Pakistan, integrated molecular frameworks research are urgently warranted to refine the early diagnostics, risk stratification, tailored interventions, and gastro cancer prophylaxis.

INTRODUCTION

Helicobacter pylori is emblematic of humanity's most successful pathogenic biota. First, it maintains a presence in the extremely acidified environment of the gastric cavity. Second, it has a long persistence. Third, it only manifests

pathogenicity in a subset of exposed hosts. For these reasons, H. pylori-associated gastric pathogenicity can be characterized as complex and modelable in studies of the interaction of the host and the pathogen. Instead of being a straightforward organ isolation infection, the staged pathogenicity of H. pylori has been known to contribute to the complexity of chronic gastritis, peptic ulcer disease, and gastric cancer; while analyses of data show a global overall reduction in the prevalence of H. pylori, the infection remains prevalent in the developing the world.[1]

Among bacteria of clinical relevance, H. pylori can be accurately characterized based on its ability to incite long-lasting, and asymptomatic acute inflammation of the gastric cavity, ulceration, and the incipient steps of malignancy found in gastric invasion, intestinal metapysis, and dysplastic atrophy. Based on various factors such as H. pylori acquisition age, strain, contemporary assessment of host immunity and environment, and treatment availability, H. pylori infection can be best described as a chronic infection with multiple progressable disease states. The infection cannot be left unattended a progression of chronic infection, while unattended it can lead to a permanent violation of public health safety.[2]

Studying these interactions are broadly applicable, improving results in diagnostics, stratifying risks, and explaining the different disease phenotypes observed among patients with similar disease states, as well as promoting the targeted prevention of gastric cancer.2 A major aspect of this conceptual and suspected laboratory battlefield is the gastric colonization. The colonization of the gastric mucosa by H. pylori is due to its acid stress tolerance, urease activity, motility and chemotaxis, membrane-bound or cell wall-bound adhesins, and mucus envelope.The continuous negotiations in the defense systems of the host and the survival of the H. pylori systems is the reason for the disease and not the toxins.[3]

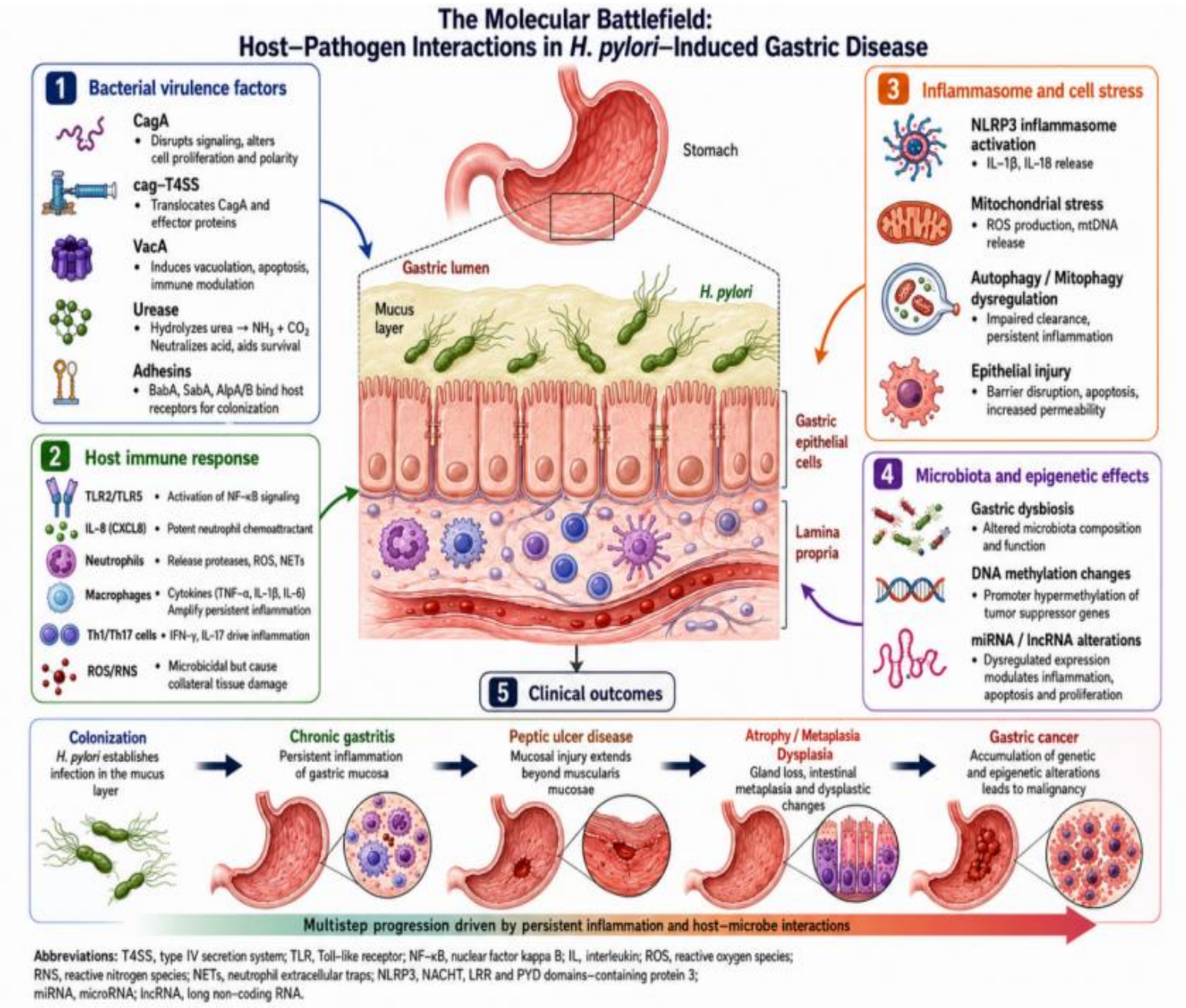

Figure 1: H. pylori evoke the host's immune response which causes inflammation and damage to the epithelium and disrupts the microbiota and induces molecular alterations which ultimately manifests as H. pylori-associated inflammation, peptic ulceration, and gastric malignancy.

The cytotoxin-associated gene A protein, or CagA, is a leading H. pylori virulence factor. CagA-positive strains are linked to the most extreme cases of gastritis, peptic ulcer disease, and gastric cancer. Once the CagA protein is injected through the H. pylori type IV secretion system, the protein causes a disruption. CagA is thought to alter epithelial cells by reprogramming them rather than simply damaging them.[4]

The CagA-secretion system is an excellent innovation because it provides a means of direct H. pylori communication with human cells. The Cag pathogenicity island (cag PAI) is the part of the H. pylori genome that provides the tools to

produce and secrete the CagA protein. The PAI is also responsible for the H. pylori induced interleukin-8.[5]

VacA, or the vacuolating cytotoxin, further complicates the pathogenic mechanism by disrupting autophagy, immune fluidity, intracellular trafficking, and the integrity of mitochondria and epithelial cells. Although vacA genes are present in many H. pylori strains, the activity of the toxin depends on the type of toxin, which creates diversity in the clinical presentation. VacA shouldn't be viewed independently of the other factors. VacA can induce CagA in the epithelial cells by hindering autophagic degradation of CagA. This shows that the major virulence factors work together and organically in the host cell.[6]

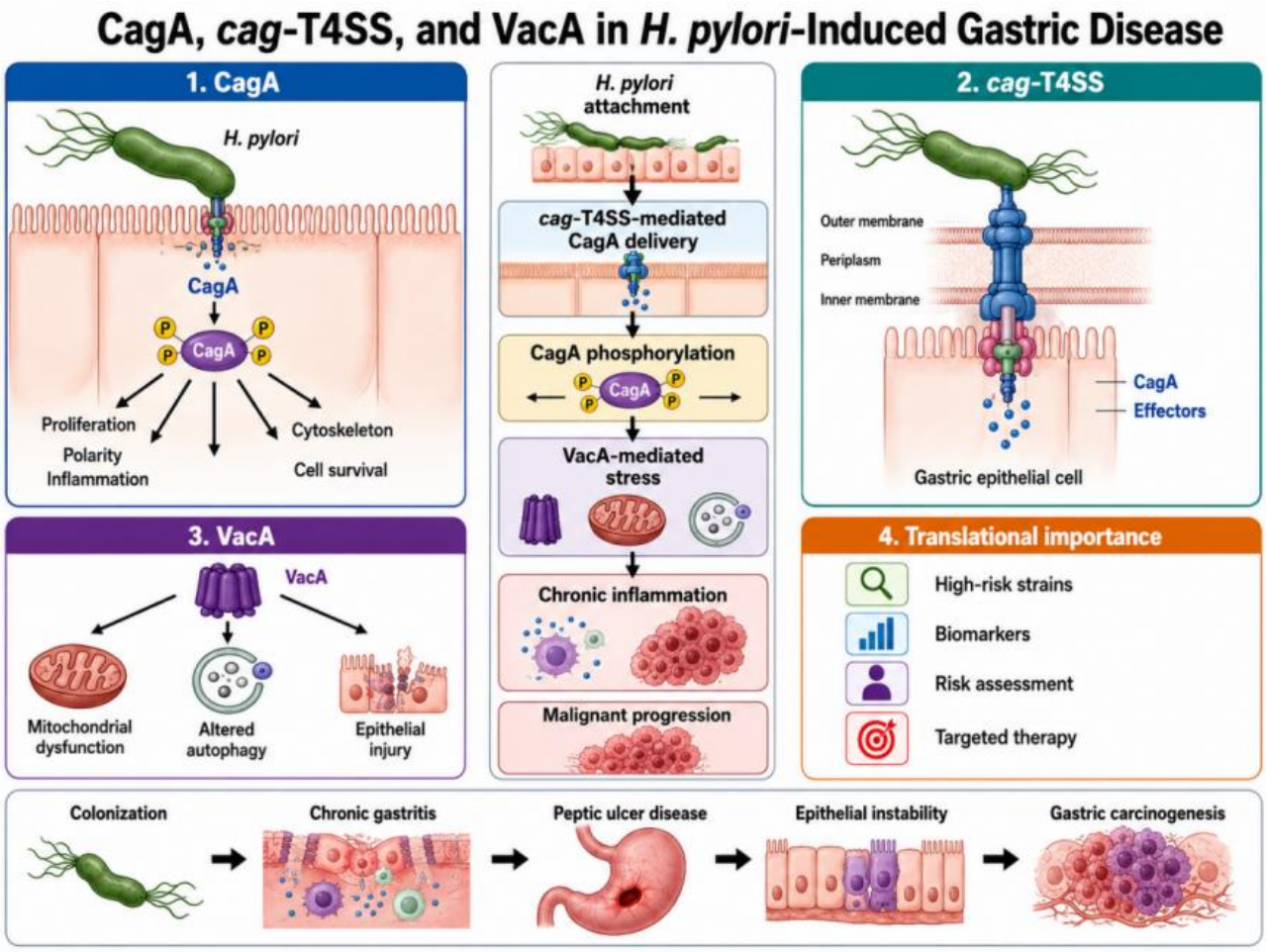

Figure 2: H. pylori damages gastric epithelial cells through the coordinated action of CagA, cag-T4SS, and VacA. This image shows the progression of the disorder from colonization to gastritis, to ulcers, and ultimately to gastric cancer.

The host immune response system serves as a barrier in this ongoing struggle, as well as being a major contributor to chronic gastritis tissue injury and H. pylori induced damage. It has been demonstrated that H. pylori induced injury activates several of the host's defensive pattern-recognition receptors across cell types from the epithelium, macrophages, and neutrophils to dendritic cells, and T helper cells and the cytokine system.[7]

A number of H. pylori studies have recently highlighted the relevance of inflammasome

signalling as the current pivot point to transition from pathogen detection to the activation of cell death and epithelial injury caused by an uncontrolled cytokine storm.[8]

The effects of the gastric microbiota, in addition to the direct virulence factors and immune responses, have emerged as yet another area of battle in H. pylori related diseases. The stomach had been regarded as almost sterile in view of the high acidity in the stomach, but a now growing number of studies show that sequencing of the genome reveals that the stomach microbiota is altered by H. pylori infection. H. pylori is able to affect the microbial composition of the gastrointestinal tract. The more recent studies show alteration of the stomach microbiata structure and biological function in patients diagnosed with gastric and duodenal ulcers.[9]

The epigenetic regulation of the long non-coding RNA pathways can help to explain the persistence of the molecular scars that are due to chronic infection, which are observable after achieving the successful eradication of a bacterial infection. This is significant as there is a genetic and an infection-mediated process in gastric cancer.The importance of this field of study for translational research is evident given the possibility to develop epigenetic signatures to detect patients at risk, even in the absence of visible malignant transformations in resource limited high infection burden settings with minimal endoscopic screening.[10]

There is now enhanced understanding of the progression from chronic gastritis to gastric cancer as a multi process and multi stage process, from bacterial virulence with respect to chronic inflammation, oxidative stress, genetic instability, increased apoptosis, bacterial translocation, to loss of immune resistance and change in microbiota. Once the threshold between reversible and irreversible precursors of inflammation is identified, improvements in screening, scheduling of curative interventions, and post eradication follow ups will be improved.[11]

Along with increasing instances of chronic infection partially due to the host and pathogen suspending the chronic infection, the increased risk for chronic stress induced inflammation and resulting epithelial inflammation, heightened instances of virulence factor as well as antimicrobial resistance all led to the change in research focus to susceptibility based, resistance determined, and anti virulence therapies along with probiotic and molecular antimicrobial therapies.[12]

This subject is relevant because the burden of the H. pylori infection is not distributed evenly across the world. Many factors, including the prevalence and burden of the disease, include sanitation, socioeconomic and overcrowding, symptoms as a child, their personal diet and the regional variety of the strain, their access to a diagnosis and antibiotics. Recent studies on the world show a decline of the burden across the world, especially in the adults, but a strong and large burden to the world across the continuum of many high burdened countries in the world. [13]

This study will try to provide a narrative of the complex mechanobiology of how the H. pylori infection occurs to establish gastric disease. Some of the factors this study will provide include all challenges of treatment, disordered epithelial signaling, and immune regulation. Such a model can assist in the identification of high-risk patients, the selection of the appropriate molecular biomarkers, refinement in the assessment of treatment options, and the development of targeted defensive measures concerning H. pylori-related gastric disorders.[14]

Overall, previous publications indicate that the development of H. pylori-associated gastric disease is not the outcome of a single cause. It is the result of the complex, multi-dimensional relationship of a highly opportunistic pathogen and a susceptible, and responsive host over a long period. The major research gap is that most studies look at the individual roles of CagA, VacA, inflammation, resistant microbiota, and resistance-related epigenetic alterations, among others, with only a few studies that focus on integrating these mechanisms into context of clinically relevant disease progression prediction frameworks.

AIMS AND OBJECTIVES

- To analyze and evaluate research literature on molecular host and pathogen response systems in

relation to H. pylori and the resulting gastric disease in order to decipher primary evidence and developmental data which can be used to formulate hypothesis frameworks relating to diagnosis and treatment.

METHODOLOGY

This systematic review examines earlier studies to identify molecular host/pathogen interactions between Helicobacter pylori and their role in gastric disorders. Main mechanisms, findings, and problem areas in relevant research are identified. We searched PubMed, Scopus, Web of Science, and Google Scholar over a four month period from Jan 15, 2026 to May 15, 2026 after the synopsis obtained the necessary approvals. We screened peer-reviewed studies published in English. Human subjects were not used, and the sample size was the number of studies examined. We screened 120 studies published between 1984 and 2025, of which we chose 75 for the final review based on inclusion and exclusion criteria. We included studies focused on gastric disorders like gastritis, peptic ulcer, and gastric cancer. We focused on bacterial virulence factors CagA and VacA, immune response, molecular mechanisms, and disease outcomes. We excluded studies unrelated to H. pylori or gastric disease, non-peer-reviewed studies, abstracts, studies in other languages, and studies lacking sufficient molecular information. We used EndNote X9 for referencing, and for extraction, organization, and documentation of findings we used Microsoft Excel and Word. We performed a descriptive synthesis to analyze the data. We identified important molecular mechanisms, contrast and describe pathogen interactions, find host mechanisms, and describe the clinically relevant findings to determine the notable gaps in research.

DISCUSSION

The results of this thesis review indicate Helicobacter pylori infection in not merely a case of bacterial colonization of the stomach, but rather a complex biological interaction of the pathogen with the gastric mucosa. From the studies examined, the pathogenic process depends on the bacteria's ability to survive, the bacterial virulence factors and the host's immune response against the epithelial cell damage and the prolonged inflammatory process. This accounts for the infection of some individuals being asymptomatic, while in others, infection may lead to processes such as gastric cancer, pyloric ulcer and inflammation.[15]

Despite declining prevalence in certain areas, H. pylori continues to be a global health concern. Evidence shows that infection rate drops do not eliminate the health risks posed to individuals who are previously infected or those who have chronic infections. Persistent infections due to various socioeconomic conditions, unsatisfactory sanitation, inaccessibility to diagnostic tests, and early-childhood infection pose the greatest challenges. It is necessary to conduct molecular studies of H. pylori, given the findings of Li and others who show, on a systematic review and a meta-analysis, a significant H. pylori worldwide prevalence decline in the years between 1980 and 2022 as well as sustained public-health relevance of H. pylori bacterial infection in multiple parts of the world.[16]

Perhaps, the greatest concern of H. pylori infection is the synthesis of gastric cancer, the synthesis of which is the most significant contribution to the review. Contained in literature is the idea that the infection of the organism is either leading to gastric cancer and/or is the consequence of chronic infection that causes the longer duration of gastric cancer and/or gastric cancer is the result of a sequence of longer duration chronic inflammatory processes (questionable of the nature chronic of the inflammatory process), followed by atrophy, intestinal metaplasia, dysplasia, etc. The Gallagher fellow of the University of Mary University of Wisconsin, shows that the patterns of global infection with H. pylori and gastric cancer are of the most significant relevance of disease burden.[17]

Literature identifies CagA as one of H. pylori's most significant molecular tools. The role of CagA in the literature is significant because it operates on tissue damage and the active reprogramming of the gastric epithelial-cell signal cascades. Cover and colleagues have examined the Cag type IV secretion system and noted that strains that

contain the Cag pathogenicity island are positively correlated with a higher risk of stomach cancer, as this system transports CagA and activates inflammation to the cell.[18]

VacA contributes almost equally to the pathophysiology of H. pylori-associated gastric disease. The studies reviewed show that VacA has the ability to cause epithelial cell damage, disrupt the normal mitochondrial functions, induce an altered state of autophagy, change the immune response, and impose stress to the cell. Therefore, VacA is responsible for the exacerbation of the pathology by modern mechanisms. VacA is meaningful in this review because it presents additional host–pathogen conflict and thereby contextualizes why some infections cause greater detrimental mucosal injury. Nejati et al. noted that CagA and VacA are the two main virulence factors that are critically responsible for the development of gastrointestinal diseases.[19]

This review highlights the fact that most H. pylori virulence factors do not function independently. Several studies indicate that within the context of a gastric epithelium, CagA and VacA would be more likely to collaborate. This suggests that the understanding of disease mechanisms may be more complex than the influence of a single factor. This collaboration may be even more pathogenic than the presence of one virulence marker. Abdullah and colleagues illustrated that VacA promotes CagA accumulation and therefore, was CagA dependent, thus establishing their direct coordination in this infection model.[20]

The other main focus of literature examined is related to the host response to H. pylori infection and the role that H. pylori related harmful host response inflammation plays.The mechanisms related to the inflammatory cells and the dysregulated immune response that contributes to the defense and H. pylori related harmful host response inflammation are detailed in the context of the pathogenesis of gastric cancer by Shirani et al.[21]

The role each inflammasome plays helps us understand how the innate immune system exacerbates gastric inflammation and injury. Studies indicate that inflammasomes detect danger signals to promote cytokine stress and mediate injury. Thus, once infection occurs, a prolonged and overactive inflammasome approach exacerbates the damage and supports the merging injury of both the inflammatory response and the infection. Zheng et al. examined the function of inflammasomes within the context of H. pylori infection. Zheng et al. state that H. pylori infection causes the inflammasome to activate signaling pathways, release cytokines, and gastritis.[22]

This thesis describes the link between bacterial virulence and host-cell survival and immune evasion and “the role of mitochondria and mitophagy.” A defect and imbalance of regular mitophagy can cause oxidative stress and damage to the epithelium by injury. If the infected cells continue to live, it will still cause damage. In turn, it will help to understand that H. pylori prefers to control the host-cell receptors and not just create inflammation. Chen et al. found that once CagA causes damage to mitochondria and mitophagy, cell survival can be achieved and will help infected cells to grow, further contributing to the pathogenesis of gastric cancer.[23]

The literature that was examined also describes the role of gastric microbiota in disease caused by H. pylori. The stomach was usually regarded in terms of H. pylori plus acids, but lately, it has become evident that the larger microbial domain is of interest. H. pylori infection is capable of disrupting the gastric microbial ecosystem, and the dysbiosis may lead to inflammation and of the mucosa injury, and increase the likelihood of developing cancer.[24]

Changes in the hosting cells of the H. pylori infection are explained by the reviewed literature in terms of the alteration of the disease host, and in this case, it is the changes in the DNA methylation, the microRNA alteration, and the activity of the gene long non-coding RNA. This reviewed literature also suggests that infection mediates the changes of cellular reprogramming by the host and therefore has interaction of the H. pylori virulence with the non-coding RNAs as an epigenetic system. The authors suggest this as the key to the understanding of the disease caused by cancer of the stomachs of the hosts.[25]

Discussion of the studies reviewed shows that H.

pylori-induced gastric disease is caused by multiple interlinked factors working in a CI-like manner. Epithelial changes caused by bacterial virulence factors, long-term chronic inflammation of the gastric epithelium by sustained inflammatory process caused by the immune system, cellular stress caused by inflammasomes and mitrochondria, changes in microbiota that alter the gastric environment, and disease epigenesis. This synergism is a cornerstone of advanced gastric disease.[26]

CONCLUSION

This thesis review asserts that various forms of H. pylori-induced gastric disease are caused by colonization of the gastric epithelium and the complex cascade of long-term colonization multilateral processing of the gastric epithelium. During the process of CagA, VacA, cag-T4SS, immune activation, activation of the inflammasomes, disruption of the gastric microbiota, presence of epigenetic alterations, and development of resistance to the antimicrobial agents, the disease progresses from simple colonization of the gastric epithelium to chronic gastric disorder, ulcer disease, gastric mucosal epithelial disorder, and malignancy of the gastric epithelium. In the Pakistani setting, this review establishes a theoretical framework for future molecular research, the development of advanced methods and tools for early diagnosis, the assessment of risk, and strategies for improved cancer prevention, particularly concerning H. pylori infection.

Limitation:

This thesis review is mostly limited by the fact that it does not include new lab tests or samples from the patients or local practitioners in Pakistan. Most of the studies available treat the processes as individual mechanisms and focus on CagA and VacA, the inflammatory response, the microbiota, and the role of epigenetic changes and resistance as separate mechanisms, which impedes the development of a comprehensive model for disease progression. Additionally, many of the molecular studies are done in different laboratory and population contexts, and it is unlikely that these findings are relevant to the Pakistani population, particularly in the absence of local validation. Therefore, original research is essential to substantiate these mechanisms in the Pakistani context and to correlate them with clinical outcomes.

Recommendations:

Future studies in Pakistan should include the integrated molecular studies of H. pylori-associated gastric diseases as data describing the virulence factors such as CagA, VacA, and cag-T4SS, host's immune response, microbiota alterations, changes in the body epigenome, and the factors contributing to, and manifesting, antibiotic resistance remain to be described. Research/Cli-lab should aim to recognize high-risk H. pylori strains earlier to devise molecular markers and screening protocols to identify the patients with the maximum H. pylori-related risks for chronic gastritis, peptic ulcer disease, and gastric cancer. This review further recommends that the factors related to H. pylori disease in the Pakistani population should employ a molecular, multidisciplinary, and integrated approach, with particular focus on clinical impacts, in order to enhance disease diagnosis, choice of interventions, prevention, and follow-up.

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