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Review

Relationship Between Human Microbiome and *Helicobacter pylori*

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Abstract: The enteric microbiota influences gene expression in the colonic epithelium. *H. pylori* (Helicobacter pylori) affects gastric growth factors, cytokines, and tumor cell markers, potentially benefiting the host. The interaction between *H. pylori* and human microbiota is complex but appears beneficial in gastric disease development. This publication discusses the human microbiota, gastric microbiome, chronic *H. pylori* colonization, and the bacterium's role in gastric disease. The interplay between the gastric bacterium and human microbiota during infection is also explored. The human gut has the most abundant and complex microbial community and performs vital roles in food digestion and nutrient uptake, extraction of absorbable vitamins, and inhibition of pathogen colonization. *Helicobacter pylori* is a highly specialized human gastric pathogen, predominantly colonizing the gastric mucus layer, on or adherent to the underlying gastric epithelial cell surfaces. Many studies have suggested that the gastric microbiome is related to *H. pylori* infection, and some bacterial species can be used for the detection or diagnosis of *H. pylori* infection. Human microbiome and genome analysis has revolutionized our understanding of the intricate relationship between humans and their associated microbial communities. The integration of microbiome data has displayed promising capabilities in occult disease detection, unveiling previously hidden pathologies and providing opportunities for early intervention. These groundbreaking discoveries have paved the way for novel therapeutic strategies and a deeper comprehension of the interconnected nature of the human microbiome and overall health.

Keywords: human microbiota; *Helicobacter pylori*; gut; gastric; genome

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1. Introduction to Human Microbiome and *Helicobacter pylori*

In recent years, studies have been carried out on the relationship between the human microbiome and *Helicobacter pylori* with the help of next-generation sequencing (NGS) and mass spectrometry methods. There is a link between several unexplained diseases and *Helicobacter pylori* infection, as well as the absence of specific bacterial species in the microbiota. These results have led researchers to explore the relationship between these microorganisms further. The relationship between the strict stomach guest bacterium *Helicobacter pylori* and other gastrointestinal microorganisms living in the human body (gut microbiome) is a current curiosity. This article aims to demonstrate a possible relationship between the human microbiome and *Helicobacter pylori*, which infects humans and causes several severe diseases,

as well as a relationship with the detection of various species in the microbiota that control these potentially pathogenic bacteria using molecular techniques [1–10].

The human microbiome is a collection of microorganisms which occupy various parts of the human body, such as the skin, oral cavity, gut, and mucus. These microorganisms protect the body from pathogenic bacteria and are involved in metabolic and digestive processes. The human microbiome influences several factors such as genetics, environment, age, and diet. *Helicobacter pylori* is a Gram-negative bacillus, microaerophilic microorganism that resides in the stomach. This microorganism causes several symptoms such as gastritis, peptic ulcers, and gastric cancer and may lead to iron deficiency anemia in individuals with infection [11–20].

1.1. Definition and Components of Human Microbiome

Digestion, drug metabolism, and immunity can be affected by the human microbiota. A recent finding from brain research is that the microbiota can affect human behavior and associated psychiatric symptoms such as depression, aggression, and suicide [21]. Recently, risk reduction associated with the development of asthma allergy caused by microbiota has received increased interest. The microbiota associated with *H. pylori*-combined inflammation is also an important research area in controlling the level of associated gastric cancer. Damage to the human microbiome and therapy associated with the damage are important research topics due to the associated effects on not only the host but also the environment and disease invasion [22–31].

The human microbiome is determined by the combination of microorganisms and their genomes. There are lots of symbiotic microorganisms in the human body, and the most notable microorganisms among those are found in the intestines. The human microbiome within the human body consists of more than 10^{14} microorganisms, though the population can vary. Recently, the virome, proteome, and metabolome have also become subjects of studies associated with humans. The contents of the molecular components within these vary according to the subject. This is because the combined microbial population induced in the human body depends on the age and the condition of each subject; this leads to associating elements for a variety of diseases, such as metabolic and atopic diseases. The microbiome can be divided into the sum of bacteria, archaea, phages, protozoa, fungi, viruses, antibodies, and even gene fragments. The variation in the number of harvested microbes due to sampling methods, the environment, and the diet suggests that the genetic information of unique members should vary in each subject [32–41].

1.2. Overview of Helicobacter Pylori

The human gut microbiome is an essential factor in current clinical practice. Digestive treatments, such as digestive oils and fecal transplantation, have been associated with improvements displayed in various types of metabolic diseases, autoimmune diseases, and cancer treatment, as well as inflammatory bowel disease. Numerous epidemiological and clinical data suggest that the gut microbiome is strongly associated with *H. pylori* infection efficacy and outcomes [42].

The *H. pylori*-induced host response is central to the symptoms of dyspepsia, multiple nutritional deficiencies, and malnutrition syndromes in patients with infection [3,7]. Therefore, understanding the activity of the gut microbiome is crucial in the treatment of various *H. pylori* diseases and in the search for precise biomarkers for each clinical response [12,43–48].

Since its discovery in 1982, *Helicobacter pylori* (*H. pylori*) has been shown to be the major cause of chronic active gastritis and has a close association with peptic ulcer disease, gastric adenocarcinoma, and B-cell gastric lymphoma. Although a host immune response

such as cytokine production is necessary for the removal of *H. pylori* infection, it induces a chronic immune response in the host that inhibits the development of gastritis as well as *H. pylori* monolayer growth. *H. pylori* infection progresses to ulcers, cancer, and other chronic diseases without eradication. The number and types of lipopolysaccharide (LPS), vacuolating cytotoxin (Vac A), and cytotoxin-associated antigen (Cag A) of *H. pylori* have been identified as virulence factors that lead to diseases [49–58].

2. Methods of Studying Human Microbiome and *Helicobacter pylori*

The changes in the composition of the human microbiome under the influence of *H. pylori* activity were investigated by high-throughput next-generation sequencing of the V1–V3 regions of 16S rRNA genes (Illumina Miseq, San Diego, CA, USA). The details of the method are as follows: A mixture of PCR fragment lengths of 16s rRNA genes after the first amplification was desalted using a Minelute PCR purification kit. The second PCR was conducted using primers for the Illumina adapter A with unique index sequences. Then, the library was purified using a Minelute PCR Purification Kit, and the products were examined on a DNA 1000 chip using an Agilent Bioanalyzer (5301 Stevens Creek Blvd., Santa Clara, CA, USA) to determine the concentration and the size of the fragments. The DNA was diluted to a concentration of 2 nM, and the mixture (with an aliquot of the PhiX library consisting of 10% of the purchased library) was sequenced with Miseq using 600 cycles of a Miseq reagent Kit (GENEWIZ Germany GmbH, Bahnhofstrasse 86, Leipzig, Germany). Then, the libraries were barcoded for analysis, and the raw data were filtered and demultiplexed. The number of sequence reads obtained after filtering was in the range of 35–142 thousand. The obtained results were visualized with the use of qiime and r packages [59–68].

In the study of *H. pylori* and human microbiota, cultivation methods suffer from a number of disadvantages. They do not guarantee the detection of all cultivable species of microbiota in the human body. It is hard to analyze the occurrence of *H. pylori* in the complex population of other microorganisms because of this. Massive parallel sequencing of 16s rRNA genes is a state-of-the-art method for analyzing the human microbiome. However, its use in determining the composition of the human microbiome can lead to ambiguous or incorrect results [69–78].

Metagenomics and Metatranscriptomics

While metagenomics refers to the genetic analysis of a pool of organisms, metatranscriptomics was introduced to assess the RNA expression created within a particular sample—also from a pool of organisms. Due to the fact that metatranscriptomics is frequently used to study biofilm-expressed genes involved in microorganism colonization and virulence, the term has been embedded in different fields. Furthermore, in contrast to metagenomic profiling, metatranscriptomics offers the possibility to explore dynamic gene/transcript expression without any lab-based induction conditions. For some infectious diseases, the pathogenic organism is surrounded by the host DNA and RNA and might hamper pathogen characterization when metatranscriptomic analyses are performed [79–88].

In 2005, Gill and co-workers surveyed the combined genomes of the microbial communities residing within the gastrointestinal and oral tracts of two healthy humans using whole-genome shotgun sequencing. This work marked the first use of the terms “microbiome” and “microbiota”. In this first study, the researchers identified larger numbers of putative new genes than had been predicted based on earlier molecular methods. Moreover, they showed that the two individuals, despite having a significant fraction of shared organisms, had dramatically different gut and oral microbiomes [89–97].

3. Impact of *Helicobacter pylori* on Human Microbiome

The presence of the *H. pylori* bacterium determines the composition, balance, and activity of the microbiota, which in turn determine the metabolic capacity, immunological response, and homeostatic level in the human stomach. Due to the fact that the interrelationships among bacteria determine the burden of diseases, treatment and eradication of *H. pylori* can lead to the appearance of other chronic human diseases whose pathogenic mechanisms are yet to be certified at this time. Preventive measures, therapy development, and inoculation with gastropathogenic bacteria of the stomach and duodenum that can be obtained from guts that are directed towards matching the stomach microbiota of patients with infection are necessary measures for preventing such kinds of complications. These kinds of strategies could exploit the benefits of the balanced microbiota that is created by the presence of *H. pylori* [3,5,10,98–104].

Helicobacter pylori is a bacterium that has co-evolved with humans, and its colonization in the human stomach has been associated with most common diseases, such as peptic ulcer disease and gastric cancer. However, there is increasing evidence for a protective role against other diseases, such as esophageal adenocarcinoma, gastroesophageal reflux disease, and non-inflammatory bowel disease. The purpose of this paper is to review the most recent findings about the effect of *H. pylori* infection on human microbiome levels and composition and to argue about the potential impact of *H. pylori* on some chronic human diseases. There are microorganisms that are obligatory or facultatively present in the human stomach, such as *Candida* spp., *Streptococcus* spp., and *Lactobacillus* spp., which also have important effects at this level [3,100,105–112].

Dysbiosis and Microbial Diversity

In humans suffering from *H. pylori*-associated diseases, non-*H. pylori* microbiota changes involve abundance alteration, microbial localization, and overall diminished microbial diversity. Endoscopy has shown gastric intestinal metaplasia (GIM) and gastric mucosa-associated lymphoid tissue lymphoma (MALT) disease localization only in the corpus but not in the antrum. A statistical and spatial realigning normalization of induced co-expression modules returns significantly enriched mucosal immunity. High levels of associated classical macrophage processes reinforce an antrum–corpus regulatory axis with a signal loss in the corpus due to a decrease in the antrum–corpus ratio in the GIM and diseased tissue samples, thus potentially facilitating disease evolution. Infection with *H. pylori* appears to induce a significant reduction in the mucosal microflora [15,113–118].

Dysbiosis describes disturbed homeostasis in humans suffering from several diseases with an altered microbiota. Changes in the intestinal and oral microbiota composition have been demonstrated in major pandemics. Translating these observations into chronic latent infections faces the limitations of cross-sectional designs with distinct populations. On the other hand, chronic colonization of a variety of body habitats with a variety of pathogens, with a variety of pathways, offers a wide range of therapeutic interventional targets. Regulatory considerations and possible side effects have to be addressed, though [118–127].

4. Interactions Between *Helicobacter pylori* and Gut Microbiota

There are several controversies regarding this influence. *H. pylori* can encode protease lysine acetyltransferase, a multitasking essential gene that is part of a widespread pathway in the probiotic *Lactobacillus reuteri* with the host to improve host nutrition. Therefore, researchers believe that there could be a symbiotic relationship between *H. pylori* and gut microbiota. However, a recent study reported that the abundance of commensals did not rise, and some commensals were found to be decreased. According to the experimental results, this situation may be an adaptive event of microbiota following the eradication

of *H. pylori*. Furthermore, there was an increased abundance of *Akkermansia* in the *H. pylori*-infected group, and it was found that *H. pylori* infection could increase the gene expression ratio of *Akkermansia* rather than increase its abundance. It is also interesting that Lachnospiraceae, as a commensal negatively correlated with pathogen colonization, decreased in the colonic mucosa-associated microbiome (CMAM) after *H. pylori* eradication. How *H. pylori* affects typical commensals in the gut microbiota glove or why this effect is controversial is still poorly understood [2,10,128–134].

The human microbiome comprises diverse and distinctly distributed microorganisms, which can be influenced by *Helicobacter pylori* infection. Although *Helicobacter pylori* is known to inhabit the stomach, several studies have found the presence of *H. pylori* DNA in some feces or colon contents. Therefore, researchers have been interested in microorganism shifts between infected and non-infected individuals. At the family level, the proportion of the detected gut microbiota of end-stage renal disease (ESRD) patients with *H. pylori* infection was significantly lower than that of non-infected *H. pylori* patients. Additionally, there was a significant increase in the presence of the *Veillonellaceae* family and a significant decrease in the presence of *Bifidobacteriaceae*, whereas the *Ruminococcaceae* family was significantly increased in hemodialysis (HD) patients after *H. pylori* eradication, contrary to the *H. pylori* prevalence [49,67,135–137].

Immune Response and Inflammation

The immune response to *Helicobacter pylori* has been characterized as a non-desirable persistent response due to the failure of the immune system to solve the infection. This response is orchestrated by the host through both innate and adaptive immune mechanisms and is carried out by the activation of a complex network of a variety of types of cells from the immune system, such as macrophages, monocytes, and lymphocytes (B and T). The outcome of the immune response to *H. pylori* alternates between a protective and a pathological role. On one side, the immune response puts bacteria under control and avoids uncontrolled spreading of the infection. On the other side, the persistence of the bacteria during chronic infection results in chronic inflammation, which has been linked to different illnesses like peptic ulcer disease, atrophic gastritis, and gastric cancer.

As a master of immune evasion, *H. pylori* has developed sophisticated strategies to evade immune detection. This pathogen can actively modulate the functions of antigen-presenting cells and regulate the production of immuno-modulatory cytokines [138]. Thus, the modulation of *H. pylori*-induced immune responses attracts considerable interest. Upon infection, the host's innate immune system is the first line of defense that rapidly responds to *H. pylori* bacteria through the recognition of pathogen-associated molecular patterns by macrophages, monocytes, and dendritic cells. Once this occurs, the infected cells secrete a range of immuno-modulatory cytokines, for instance, tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), IL-6, and IL-8, some of the most important cytokines for the innate immune response. Thus, in a coordinated fashion, these chemokines orchestrate a local immune response that includes chemotaxis of PMNs to the site of infection and promote blood vessel permeability and leakage to attract a variety of immune cells. From that point on, these defense cells can perform phagocytosis of the infecting bacteria, thus reducing their spread through the epithelial lining of the stomach. To further develop a targeted and adaptive immune response toward the pathogen, a more specific recognition from both the T and B lymphocytes is needed. This is carried out through a series of extremely sophisticated mechanisms called antigen presentation, where peptide antigens derived from invading pathogens are presented in association with a major histocompatibility complex, MHC [139].

From then on, these antigen-presenting cells (APCs) activate CD4+ T lymphocytes by engagement of the T-cell receptor (TCR) with the peptide–MHC complex as well as the co-stimulatory signal CD28-CD80/86, expressed in T cells and APC cells, respectively. Subsequently, these activated CD4+ T helper cells (Th) assist during the activation of B cells, thus enhancing the production of specific antibodies against the pathogen.

Cytokines play a crucial role in shaping the immune response against *Helicobacter pylori*. Among the plethora of cytokines known so far, several have emerged as key players in the modulation of the immune response to this bacterium. Infection with *H. pylori* induces an increase in cytokines, including IL-1, IL-6, and TNF-α, which are proposed to play pivotal roles by promoting inflammation in the presence of infection. IL-1 is known to induce inflammation through different pathways and cell types. IL-6 is a pleiotropic cytokine that plays pivotal roles in regulating immune responses by interacting with various cell types. TNF-α, a potent pro-inflammatory cytokine, is produced by various immune cells and plays critical roles in promoting inflammation. Interactions between these cytokines and various immune cells ensure the generation of effective responses against pathogens.

Moreover, the ability of individual cytokines to elicit several outcomes has also been proposed to be the basic principle of a biphasic curve in the determination of disease outcomes, in which either too little or excessive inflammation leads to disease [139]. This cytokine dichotomy suggests that there are protective and pathogenic aspects of cytokine function depending on the context. The importance of specific cytokine signaling pathways, however, is also emphasized because they influence the survival and propagation of *H. pylori* in vivo and highlight the regulatory mechanisms utilized by the bacterium to fine-tune the response. Inflammatory cytokines play an important role in recruiting immune cells to the site of infection and in stimulating these cells to generate a protective immune response. When it occurs, *H. pylori* enters the gastric mucosa, where it survives due to its ability to subvert immune recognition and generate only a weak, chronic immune response. *Helicobacter pylori* infection elicits a strong innate immune response in the lamina propria with prominent upregulation of chemokines in the gastric mucosa. However, the inflammatory response is unable to clear the bacterium, and chronic infection is usually established [140].

However, the commensal microbiota may act as a modifier of the host's responses to an infectious pathogen, through either direct competition with *H. pylori* or through passive modulation of the outcomes of the microbiome subcommunities in the stomach, mediated solely by the shifting of commensal populations during infection. Indeed, the commensal microbiota is dysbiotic compared to infection-free counterparts. The abundance of a commensal discovered to be significantly correlated during the dysbiotic period is affirmed in an unexpected manner. Therefore, the manipulation of the replication of the commensal, or clearing the commensal when it does not thrive, in either control mouse is feasible, facilitating the intrinsic role of the commensal in modifying *H. pylori*-induced gastritis severity. In conclusion, in two mice, two *H. pylori* strains exhibit different pathology severities, where the differences are controllable through the degree of infection and are likely not due to silencing determinants that may enable pathology in TO. The force underlying the host inflammatory support selects for different *H. pylori* genotypes in different contexts. The effect can be altered by manipulating the commensal microbiota or directly competing with the infection [112,141–150].

The scrambling bacteria lead to the eradication of commensal microbiota located in the stomach, including *H. pylori*, especially in the implemented or chronic inflammatory sites. Dysbiosis is the outcome of the loss of host–microbiome homeostasis and leads to moderately complex alterations in the composition of the luminal and mucosal microbiomes. Various connections between diseases by modifying the microbiome have been reported.

Chronic gastritis is known as a typical inflammatory disease caused by *H. pylori* infection, characterized by inflammation and immune cell invasion in various sites, both in the corium and the basal and neck mucus areas. Despite all of these fears of facilitating the pathways linking *H. pylori* infection with gastritis and neoplastic sections of the development, and the long-established role of inflammation in tumorigenesis, the mechanisms leading from the inflamed microenvironment to disease are not genuinely understood [3,105,151–156].

5. Role of Human Microbiome in *Helicobacter pylori*-Associated Diseases

Microbial interactions in *H. pylori*-associated diseases: *Helicobacter pylori* not only directly or indirectly damages the mucosa of the stomach and duodenum but also affects the whole body. The disruption of the balance of the microecology also affects the course of the disease. It is known that a long infection with *H. pylori* can affect the natural microecology of the stomach. However, little is known about the characteristics of the stomach's microbiome and the interactions. For example, there is no clear cause of gastric carcinogenesis as a combination of multiple microorganisms rather than a single *H. pylori*. Alcohol suppresses gastric microbiota presentation. Zhong Rongrong and Timothy Lu found that alcohol can benefit *H. pylori* colonization by changing the gastric microbiota. From this result, it is not known whether alcohol influences commensal bacteria or harmful bacteria. However, the authors recognized that this is not a breakthrough. They also believe that harboring a drug-resistant supermannose morphology contributes to this, but it is impossible to observe the niche size during this colonization and the relationship between a microbe and the environment it carries. At present, research on the human gastrointestinal flora is only at the beginning of the process, and the relationship between *H. pylori* and the corresponding natural microecology is much more critical [150,151,156–160].

Overall association between diseases caused by *H. pylori* and entire microbiome: In modern times, several other microbes have rewritten the natural microbial flora of humans and aggravated it with various diseases. Individual associations of *Helicobacter pylori* with diseases are good, but many diseases have complex microbial associations. More recently, increased knowledge of microbiota using metagenomic data has led to an understanding of the relationship between *H. pylori* and the human microbiome. An example of a disease associated with the microbiome is gastric cancer. *H. pylori*, which is very abundant in the stomach, is a low-abundance microbe in gastric cancer but has a positive association with *Synergistales* and *Balneimonas*. On the contrary, the proportions of commensal bacteria, which are usually abundant, such as *Proteobacteria* and *Firmicutes*, are reduced. Therefore, the specific association with the stomach has a weak relationship with bacteria but a complex relationship with many microorganisms. However, the complex relationship changes over time to a simple structure due to bacterial antagonism or cooperation [161–163].

The stomach's acidic environment is considered to be very autologous, thought to render it sterile. However, certain factors in the stomach are potent indicators of the behavior of inflammation. These include interleukin 1β, in particular the polymorphism that increases IL-1β expression, transforming growth factor β1 (TGFβ1), the inflammation and lymphoma protein 1-beta (MAL), and the cationic trypsinogen it regulates, particularly in its homozygous form, which induce tumors in the gastrointestinal tract. Such proteins can be considered potent indicators of the behavior of inflammation in mainly young adults with chronic *H. pylori* infection. The elderly, patients with long-standing severe gastric abnormalities, "blood group X" subjects, and individuals with insulin-dependent diabetes are also predisposed to developing malignancies of the intestinal tract. The behavior of the infection during the patient's lifetime could determine the final outcome. The recognition of the entity of benign diseases has become of primary importance in establishing an itinerary for the primary and secondary prevention of gastric cancer [164–171].

Chronic infection with *Helicobacter pylori* is the leading risk factor for peptic ulcers and gastric cancer, causing an estimated 75% of the total ulcer and gastric cancer burden in infected populations. Research into understanding and dissecting the mechanisms behind gastric lesions supports the need to focus attention on the impact of the human microbiome in the progression to disease and exacerbation of inflammation. Understanding the role of the microbiome as a contributory factor in gastritis and peptic ulcers is achieved by focusing on the chronicity of *H. pylori* infection. Chronic infection with *H. pylori* is a necessary condition for both the development of peptic ulcers and the progression of gastritis towards gastric cancer [172–178].

6. Therapeutic Strategies Targeting the Microbiome in *Helicobacter pylori* Infections

With this in mind, it should come as no surprise that increasing attention is being paid not only to characterizing the composition of the human microbiome in different niches encountered in a human body but also to understanding how these organisms interact with their host and the potential consequences of disrupting these host–microbiome interactions. The ultimate aim is for the knowledge to help drive our attempts to develop new therapeutic strategies that can modify host–microbiome interactions, with the ultimate goal of steering the microbiome to in turn reshape the consequences on health and disease outcomes [179].

An ever-growing body of evidence from research in the modern life sciences, especially from the rapidly evolving fields like microbiology and genomics, has clearly pointed out the critical roles that the human microbiome is playing in modulating the health of the host. Moreover, these commensal microorganisms have been found to be able to shape the host's susceptibility to various types of disorders, from obesity to metabolic syndrome, and immunological diseases to cancers [180–187].

In this review, we summarized the well-documented relationship between *Helicobacter pylori*, a pathogen which is well recognized as being associated with an increased risk of developing gastric diseases, and the human microbiome living in the stomach, as well as potential therapeutic strategies directly targeting *H. pylori* and especially those targeting the human stomach in responding to the infection [188–193]. Because the human-associated microbiome has increasingly been found to play a variety of roles in modulating human health and diseases, a mechanistic understanding, both directly and indirectly, of the interplay between the human microbiome and the host immune system has opened up potential avenues for designing novel therapeutic strategies aiming at modulating the microbiome to in turn reshape the immune mediator-associated consequences and, as such, influence organism health and disease outcomes [194–196]. Various studies have explored therapeutic strategies targeting the microbiome in *Helicobacter pylori* infections in humans and their implications [197–200].

Probiotics and Antibiotics

Anti-*H. pylori* treatment failure is associated with complex microbial characteristics and resistance. Different microbial abnormalities may reflect various clinical features of *H. pylori* infection, with diverse human microbiota. Therefore, recruiting appropriate probiotics designed to shift the patient's disrupted dysbiosis may improve the efficacy of *H. pylori* eradication therapy. Several probiotics are associated with increasing and improving the success rate of *H. pylori* therapy. The most well-characterized probiotics, secreting lactic acid and enhancing the activity of metabolites against *H. pylori* infection, are *Lactobacillus*, *Saccharomyces boulardii*, and *Bifidobacterium*. Scientists are also attempting to develop engineered probiotics that can deliver antimicrobial proteins specifically targeting *H. pylori*. The concept is based on modifying probiotics with drug plasmid vectors [201–208].

Probiotics have been pursued as a complementary treatment to antibiotics in the management of *H. pylori* infection. In general, probiotics have been demonstrated to have a very low adverse effect profile, as they are non-pathogenic, safe, affordable, and easily available for broad population use. Probiotics have been postulated to have a role in the eradication rate, in reducing adverse events of common anti-*H. pylori* drugs, and in preventing new infections. They have the potential ability to prevent gastric inflammation and foster post-microbiota restoration [208–214].

7. Future Directions and Research Challenges

In addition, the manipulation of GI microbiota through proper environmental intervention, such as antibiotics, infection with probiotics, prebiotics, diet, and fecal transplants, can and will inform the types, levels, diversity, and stability of GI microbiota for the prevention and mitigation of *H. pylori*-associated pathophysiologies. These studies will guide the formulation of research hypotheses for direct mechanistic gut interaction studies that will enable researchers to elucidate the basic principles underlying the *H. pylori*–gastrointestinal metaorganism relationship for the application of precision intervention, prevention, and treatment of dysbiosis of the host–microbiome ecosystem [215–222].

The establishment of a standard operational protocol is critical for the design of morbidity and mortality studies and comparisons among different clinical research laboratories. Longitudinal analyses of GI metaorganism ecology, the types and levels of *H. pylori* strains, and the diversity, distribution, and function of gastric, liver, small intestine, and colon microbiota are focusing on the development of age-associated morbidities and will help to disentangle the role of *H. pylori* in the gastrointestinal system [223–232].

Collectively, evidence supports both beneficial and pathogenic roles of *H. pylori*-associated microorganisms, including oral, esophagus, stomach, intestine, and colon microbiota. Current "omics" approaches, including metagenomics and metabolomics, have been adopted to investigate the complex microbiota composition of the stomach. This approach, in conjunction with improved in vitro gastrointestinal models and multimodality imaging technologies, should enhance our ability to dissect the experimental cause and effect, as well as aiding therapeutic strategies [233,234].

Precision Medicine Approaches

Despite the relatively new nature of such studies, clear and replicable relationships have been defined in at least three areas—responders to immunotherapy, associations between the gut microbiome and subsequently developing immunotherapy toxicities, and associations between the gut microbiome and therapeutic response in patients with leukemia. Associations have been classified according to disease risk, which thus allows for enhanced screening and prophylaxis that may reduce toxicities. As technology continues to improve, the microbiome will be an increasingly effective lens to use when approaching all aspects of precision medicine, including predicting, identifying, and treating disease, whatever form it takes and in whatever part of the body it is found [235–244].

As research into the human microbiome expands, considerable effort is being placed on understanding how perturbations to the communities of our microbiome caused by environmental factors (like diet or exposure to pharmaceuticals) are associated with disease. Several recent studies have linked changes seen in microbiomes from different body sites with disease, including ulcerative colitis, colorectal cancer, and *Clostridium difficile*-mediated colitis. These studies continue to add weight to over a century of research connecting the human microbiome with human health. Precision medicine approaches are already being studied with respect to associations between specific microbiome community

constituents, functions, or biological molecules and responses to cancer treatments and their toxicities [245–251].

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