American Journal of Medicine and Medical Sciences 2025, 15(10): 3620-3623
DOI: 10.5923/j.ajmms.20251510.73

The Role of the Intestinal Microbiome in the Development of Stomach Diseases

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Abstract The authors analyzed new information on the role of the gut microbiome in the development of gastric diseases. Microbiome research is a rapidly developing area in modern medicine. H. pylori is a recognized risk factor for gastric cancer. In recent years, mounting evidence has emerged that bacteria other than H. pylori and their metabolites also contribute to gastric carcinogenesis. Research suggests that various components of the gastric microbiome may influence the development of gastric cancer, but the role of individual pathogens remains unclear. 16S rRNA sequencing was also used to study microbiome composition and its association with safety parameters, including the risk of gastric cancer. Studying the role of the gut microbiome in the development and progression of gastric diseases may lead to improved prevention, diagnosis, and treatment.

Keywords H. pylori, Gut microbiome, Gastric cancer, 16S rRNA sequencing, Chronic gastritis, Diagnostic biomarkers

1. Introduction

In 2022, 20 million cases of cancer and 9.7 million deaths were registered worldwide. Stomach cancer is the fourth most common malignant carcinoma and the second leading cause of cancer death. An estimated 989,000 new cases of stomach cancer are registered annually. In our Republic, stomach cancer ranks second in the structure of oncological diseases and the incidence rate is 6.8 cases per 100,000 [24]. The development of cancer is caused by several factors, and one of the main ones is the confirmed presence of Helicobacter pylori (H. pylori) [7]. However, many researchers believe that in addition to H. pylori, other bacteria can also provoke the development of chronic inflammatory changes in the gastric mucosa and even contribute to the development of stomach cancer. It has been proven that the development of atrophic gastritis should be accompanied by a decrease in acid production in the stomach, which, in turn, leads to changes in the microbiome [19]. Numerous studies have recently shed light on the relationship between the gastric microbiome and gastric cancer [2,12]. This review will examine the relevant literature in the field of gastric cancer and its microbiome [20]. Although H. pylori is the most important bacterial carcinogen in gastric cancer (GC), GC can transform even after H. pylori is eradicated.

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Received: Sep. 23, 2025; Accepted: Oct. 25, 2025; Published: Oct. 31, 2025
Published online at http://journal.sapub.org/ajmms

The development of the most common form of GC (i.e., the intestinal subtype) is a multistep process known as the Correa cascade, which begins with precancerous gastritis, intestinal metaplasia (IM), and ends with dysplasia [5]. Chronic gastritis is an early manifestation of persistent inflammation caused by H. pylori infection. As the disease progresses, damage to gastric epithelial cells can lead to the development of GC. H. pylori has been listed as a type I carcinogen by the World Health Organization (WHO) [18]. Therefore, detection and eradication of H. pylori at an early stage of infection can prevent gastric cancer and other gastrointestinal diseases. H. pylori is a well-recognized risk factor for gastric cancer. In recent years, increasing evidence has emerged that bacteria other than H. pylori and their metabolites also contribute to gastric carcinogenesis [6]. More than half of the world's population is infected with H. pylori, which can alter gastric acidity, changing the profile of the gastric microbiome, leading to H. pylori-associated diseases [4].

Research shows that various components of the gastric microbiome may influence the development of gastric cancer, but the role of individual pathogens is unclear. 16S rRNA sequencing is also being used to study the composition of the microbiome and its association with safety parameters, including the risk of developing gastric cancer. 16S rRNA is a unique and highly conserved region of the nucleotide chain of all bacteria, which is traditionally used to identify bacteria [15]. This method is considered the "gold standard" for the most comprehensive analysis of microbiome composition. Therefore, elucidating the contribution of the gastric microbiome to the development and progression of gastric cancer can lead to improved prevention, diagnosis, and treatment [1].

2. Materials and Methods

The microbiome of a healthy person contains over 10,000 different microbial species. The microbiome is the collection of bacterial genetic material. Gut bacteria contain approximately 150 times more genes than humans. The specific mechanisms contributing to interindividual differences in the composition of the gastric microbiome are poorly understood. The composition of the microbiome is influenced by the mode of delivery (in infants), age, gender, ethnicity, diet, lifestyle, geography, antibiotic use, use of proton pump inhibitors (PPIs) or histamine H2 receptor antagonists, and the presence of H. pylori. The acidic environment of a healthy stomach prevents bacterial overgrowth and reduces the risk of infection. Long-term treatment with PPIs or H2 antagonists reduces gastric acid secretion, leading to bacterial overgrowth. Antibiotic use, immunosuppression, and gastric pH > 4 have been found to be associated with reduced bacterial diversity in the stomach. Interestingly, a study of the gastric microbiome in twins showed that genetic background had no effect on the structure of the gastric microbial community; similar results have also been obtained for various niches of the human body [16].

The microbiome influences cancer development by modulating the local tumor microenvironment through its effects on tissue remodeling and mucosal immunity. Angiogenesis, one aspect of tissue remodeling that occurs during tumorigenesis, ensures adequate blood flow, which is integral to tumor persistence and proliferation. Although direct links between endogenous bacteria and tumor-associated angiogenesis have not been documented, the microbiome is essential for normal vasculature development in the intestine. Moreover, in the context of infection, microbial products such as lipopolysaccharides interact with Toll-like receptors, promoting angiogenesis, an effect that is enhanced by damage-associated molecular patterns that may also be present in the tumor microenvironment [14].

Over the past decade, the development of next-generation sequencing (NGS) technologies has significantly improved the accuracy of taxa detection and identification, ultimately leading to deeper profiling of the gastric microbiome and the study of its interactions with the host. Among NGS methods, 16S rRNA sequencing is widely used, as the 16S gene contains both conserved regions supporting phylogenetic classification at the typical level and rapidly evolving regions suitable for more detailed taxonomic classification [5].

Chinese researchers have identified significant differences in the gastric microbiota between patients with gastric cancer and non-cancer patients, suggesting that the microbiota may play a role in tumor development. A meta-analysis, "Using Existing 16S rRNA Microbial Data to Establish a Diagnostic Biomarker in Chinese Gastric Cancer Patients," analyzed existing 16S rRNA microbial data to find combinations of five genera that showed good performance in distinguishing gastric cancer from non-cancer patients across multiple sample types [8]. Research has shown that microorganisms in the upper gastrointestinal tract may contribute to cancer development by promoting inflammation or interacting with pathogens. Therefore, investigating microbiome-based diagnostic markers for gastric cancer in the population is of great importance for the identification, prevention, and treatment of gastric cancer [21].

16S rRNA is a component of the ribosomal 30S subunit, which is highly conserved and specific to prokaryotes. 16S rRNA variable region sequencing is currently the most widely used method for studying microbial diversity. This study was the first to examine the main characteristics of the flora in GC compared with non-cancerous samples [16]. Alpha diversity indices (evenness index, Shannon index, and observed features) were increased in GC from the Matched group, but evenness and Shannon indices were decreased in GC from the Unmatched group after accounting for control factors [21]. Current studies have not consistently concluded the relationship between microbial diversity and gastric disease status, and another study showed that the diversity and abundance of the gastric microbiome were higher in tumor tissues than in non-tumor tissues. However, the diversity and richness of peritumoral and tumor tissues were reduced in 276 patients with GC compared with non-tumor tissues [10]. This study may partially explain the inconsistent alpha diversity results in previous studies, which may be due to controls being from the same individual or from different individuals. LEfSe analysis revealed that six genera Streptococcus, Peptostreptococcus, Selenomonas, Pseudomonas, Prevotella, and Fusobacterium—may have potential diagnostic biomarkers for distinguishing gastric cancer from noncancerous gastritis. Interestingly, all these bacterial genera are oral microorganisms, suggesting that the oral flora plays an important role in the development of gastric cancer [5].

A prospective, multicenter clinical study examined the bacterial microbiome based on the 16SrRNA gene amplicon in 30 homogenized and frozen gastric biopsy specimens from eight locations in Austria [14]. In this scientific study to characterize the human gastric microbiome structure and its association with H. pylori infection, gastric biopsies from a cohort of 30 patients prospectively evaluated for H. pylori were analyzed with and without detection of the CagA gene. Previous studies of the human gastric microbiome indicate a distinct gastric microbiome pattern with dominant phyla Actinobacteria, Bacteroidetes, Firmicutes, and Proteobacteria and the most dominant genus Streptococcus. The taxa identified in this dataset are consistent with these previous studies from phylum to genus level. According to the results of this study, culture-based approaches predominantly detected Streptococcus, Neisseria, Klebsiella, and Lactobacillus, with Streptococcus (8.61% of all samples) and Neisseria (1.13% of all samples) confirmed as the dominant taxa. This study is notable for its prospective design, multicenter sample collection, and the availability of multiple clinical data from probands [1].

3. Result and Discussion

A subsequent study from Chin Med Sci J [17] assessed the gastric microbiome in patients with chronic superficial gastritis (CSG) and intestinal metaplasia (IM) and examined the effect of H. pylori on the gastric microbiome. Gastric mucosal samples were collected from 54 patients with CPH and CM, and the patients were classified into the following four groups based on H. pylori infection status and histology: H. pylori-negative CPH (n=24), H. pylori-positive CPH (n=14), H. pylori-negative CM (n=11), and H. pylori-positive CM (n=5). The gastric microbiome was analyzed using 16S rRNA gene sequencing. The results showed that the abundance and diversity of gastric microbes were lower in H. pylori-infected patients, regardless of CPH and CM. Compared with the H. pylori-positive CPG and H. pylori-positive CM group, the relative abundance of Neisseria, Streptococcus, Rothia, and Veillonella was higher in H. pylori-positive CM patients than in H. pylori-positive CPG patients, particularly Neisseria.

Another study [3] aimed to investigate changes in the bacterial metagenome before gastric cancer and develop a microbiome-based prognostic model for accurately classifying patients at risk for gastric cancer. Bacterial 16S rDNA was sequenced from 89 gastric antral biopsies obtained from 43 participants.

Microbiome components, particularly H. pylori, contribute to the initiation and dissemination of gastric cancer carcinogenesis. In this study, the bacterial composition of the gastric mucosa was characterized using 16S rRNA amplicon sequencing, revealing that the gastric mucosa is predominantly composed of groups of the phyla Proteobacteria and Firmicutes. Beneficial bacterial taxonomic features, such as lactic acid bacteria of the genera Lactobacillus and Bifidobacteria, were reduced in CM and CPH [22].

Other studies conducted in patients after H. pylori eradication found that "The gastric microbiome after H. pylori eradication modulates pro-tumorigenic processes and is associated with the risk of gastric cancer" [23]. Patients after H. pylori eradication were divided into three subgroups based on the microbial composition revealed by 16S RNA sequencing. One dysbiotic group, enriched in Fusobacterium and Neisseria species, was associated with a significantly higher incidence of gastric cancer. These species activated pro-tumorigenic pathways in gastric epithelial cells and promoted inflammation in the mouse stomach. Sugar chains that make up gastric mucin attenuate host-bacteria interactions. Metabolites of Fusobacterium species were genotoxic, and the presence of bacteria was associated with an inflammatory signature and a higher tumor mutational burden. A study by Olabisi Oluwabukola et al. involved 16S rRNA gene analysis of gastric mucosal samples from 81 cases, including superficial gastritis (SG), atrophic gastritis (AG), intestinal metaplasia (IM), and GC from China, to determine mucosal microbiome dysbiosis at different stages of GC [11]. Five GC-enriched bacterial taxa, whose species identification corresponded to Peptostreptococcus stomatis, Streptococcus anginosus, Parvimonas micra, Slackia exigua, and Dialister pneumosintes, had significant centrality in the GC ecological network ($p < 0.05$) and classified GC from SG with an area under the receiver operating curve (AUC) of 0.82. Moreover, stronger interactions between gastric microbes were observed in H. pylori-negative samples compared to H. pylori-positive samples in PG and CM. The fold changes of selected bacteria and the strength of their interactions were successfully validated in an Inner Mongolia cohort, in which five bacterial markers differentiated GC from PG with an AUC of 0.81. Another study [13] examined endoscopic biopsy specimens from patients with superficial gastritis, atrophic gastritis, intestinal metaplasia, and gastric cancer (~20 patients in each group) and found that gastric mucosa in cancer had marked differences in the microbiome compared to the other groups, particularly an increased presence of oral bacterial species such as Peptostreptococcus stomatis and Dialister pneumosintes.

4. Conclusions

1. The ability of microbes to damage DNA and genomic instability, both directly and through DNA damage, makes them a potential risk factor and therapeutic target.
2. Studying the gut microbiome in the development and progression of gastric diseases may lead to improved prevention, diagnosis, and treatment.
3. Studying the gut microbiota in gastric diseases may soon enable personalized medicine tailored to the microbiome of each patient.

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