Microb Health Dis 2024; 6: e1031

HELICOBACTER PYLORI AND THE MICROBIOME IN GASTRIC CANCER DEVELOPMENT AND TREATMENT: A YEAR IN REVIEW

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Abstract – Gastric cancer remains a highly common and deadly disease. In the microbial world, *Helicobacter pylori* infection is the major risk factor that initiates a cascade of inflammatory responses and genetic alterations that drive gastric cancer development. In the context of chronic inflammation mediated by *H. pylori*, some patients may develop intestinal metaplasia, a lesion that is associated with an increased risk of developing gastric cancer. However, there is increasing evidence that, in addition to *H. pylori*, the non-*H. pylori* microbiome also plays a role in gastric carcinogenesis. Furthermore, the microbiome may influence the gastric tumor microenvironment and modulate response to treatment, in particular, treatment with immune checkpoint inhibitors. This article highlights research related to these topics published between April 2023 and March 2024. The integration of findings on the complex interplay of *H. pylori* and the microbiome in cancer initiation and progression will be crucial for the development of more effective prevention and therapeutic strategies.

Keywords: Gastric cancer, *Helicobacter pylori*, Microbiome, Intestinal metaplasia, Immunotherapy.

INTRODUCTION

Gastric cancer ranks as the fifth most incident and deadly cancer worldwide, with 968,350 new cases diagnosed in 2022 and 659,853 deaths in the same year, according to the most recent GLOBOCAN data[1]. The development of gastric cancer is closely related to *Helicobacter pylori* infection, which is considered the main risk factor for this disease, accounting for approximately 90% of non-cardia cancers worldwide[2,3]. A recent systematic review and meta-analysis on the temporal trends of the prevalence of *H. pylori* infection during the last 40 years has shown a decline in the global prevalence of the infection from 58.2% between 1980 and 1990 to 43.1% between 2011 and 2022[4]. Emerging evidence indicates that eradicating *H. pylori* lowers the risk of gastric cancer in healthy individuals and reduces the incidence of metachronous gastric neoplasia in patients who

have undergone endoscopic resection of dysplastic lesions[5,6]. This supports the hypothesis that *H. pylori* treatment can serve as a preventative measure against gastric cancer.

METHODS

For this special issue, we have highlighted selected research published in the last year (between April 2023 and March 2024) related to the following main topics: *H. pylori* infection in carcinogenesis, the non-*H. pylori* gastric microbiome in gastric carcinogenesis, the microbiome in the gastric tumor microenvironment, and the impact of the microbiome in gastric cancer immunotherapy.

Helicobacter pylori Infection in Carcinogenesis

Helicobacter pylori infection and intestinal metaplasia

H. pylori is the principal etiologic factor for intestinal metaplasia (IM) of the stomach, which is associated with an increased risk of gastric cancer development[7]. Whether gastric IM represents a direct precancerous lesion or a paracancerous condition merely resulting from tissue damage from *H. pylori* and chronic inflammation remains a subject of debate[8]. Takeuchi et al[9] explored the precancerous nature of IM by analyzing epigenetic alterations. They demonstrated that gastric crypts with IM had extensive DNA hypermethylation in promoter CpG islands, including hypermethylation of tumor suppressor genes and cancer risk marker genes. This IM-specific methylation profile was observed in gastric tumors at a frequency higher than that predicted based on the proportion of IM cells in the background gastric mucosa, supporting the precancerous nature of IM. IM crypts and organoids had high expression of the nitric oxide synthase 2 (NOS2), and induction of NOS2 in normal cells was responsible for increased DNA methyltransferase activity and for aberrant DNA methylation. IL-17A, which was expressed in gastric biopsy samples of *H. pylori*-infected patients, upregulated NOS2 in IM-derived organoids. The authors suggest that IM cells have a precancerous nature with a higher likelihood of transforming into cancer cells and aberrant DNA methylation caused by abnormal NOS2 expression mediated by IL-17A in the context of *H. pylori* infection.

O'Brien et al[10] described metaplastic pit cells as a precancerous cell type that is expanded by *H. pylori*-mediated inflammation. They characterized gastric cell populations by single-cell RNA-sequencing (sc-RNA-seq) of a transgenic mouse model in which *H. pylori* infection together with KRAS activation (Hp+KRAS+) lead to severe inflammation, changes in expression of markers of metaplasia, and increased cell proliferation and dysplasia in comparison to Hp–KRAS+ mice[11]. An expanded population of metaplastic pit cells characterized by *MUC4* and amphiregulin expression in Hp+KRAS+ mice associated with lamina propria macrophage and T cell-mediated inflammation was identified. Treatment with an immunosuppressive drug reduced these cell types and MUC4 expression and also reduced MUC4 expression in mice undergoing *H. pylori* eradication. In patients with metaplasia and gastric cancer, metaplastic pit cells were also detected.

Liang et al[12] proposed that *H. pylori* contribute to IM development by altering the kynurenine pathway of tryptophan metabolism. They identified xanthurenic acid (XA), a product of the kynurenine pathway, as a differently expressed metabolite in cancer cells treated with *H. pylori* and its CagA and VacA virulence factors. Increasing doses of XA, as well as *H. pylori*, led to the upregulation of CDX2, MUC2, and Villin mRNA expression. The authors observed increased expression of kynurenine aminotransferase II (KAT2), which regulates the levels of XA, in patients with *H. pylori* infection and IM. Inhibition of KAT2 abrogated *H. pylori*-mediated upregulation of CDX2 and MUC2 expression *in vitro* and reduced their expression in the gastric mucosa of infected animals. *H. pylori*-induced expression of KAT2 was attributed to activation of Interferon Regulatory Factor 3 (IRF3) signaling. The increase in the expression of KAT2, CDX2, and MUC2 in *H. pylori*-infected mice was reversed by treatment with an IRF3 inhibitor. In gastric cells of patients with IM, IRF3 phosphorylation was positively correlated with CDX2 expression. The results suggest that *H. pylori* activates IRF3 signaling to promote the KAT2-mediated kynurenine pathway, leading to XA production, which induces CDX2 expression in gastric epithelial cells.

Helicobacter pylori-mediated mechanisms of gastric carcinogenesis

CagA is a secreted effector protein of the *H. pylori* type IV secretion system (Cag T4SS) with a major impact on gastric carcinogenesis[13,14]. Takahashi-Kanemitsu et al[15] identified a potential mechanism through which CagA may contribute to gastric cancer development. Using *Xenopus laevis* embryos with ectopic expression of CagA, the authors showed that CagA disrupts a non-canonical Wnt pathway that mediates planar cell polarity (Wnt/PCP), a process that contributes to the shaping and structuring of tissues during development. CagA physically and functionally interacted with VANGL1/2 proteins, which are main components of the Wnt/PCP pathway, and inhibited their interactions with the Dishevelled protein, resulting in activation of the downstream effectors of the Wnt/PCP signaling, linked to gastric epithelial stem cell neoplastic transformation. In a transgenic mouse model with inducible expression of CagA in stomach epithelial cells, there is an increase in the length of pyloric glands, in parallel to hyperproliferation of epithelial cells at the base of the pyloric glands, repressed cell differentiation, and mislocalization of VANGL1/2. This points the Wnt/PCP signaling pathway as a potential target for gastric cancer prevention mediated by *H. pylori* CagA.

Other mechanisms link *H. pylori* to the development of gastric cancer, including bacteria-mediated alterations in DNA repair systems and DNA damage in the form of DNA double-strand breaks[16]. Using murine-derived antral and corpus organoids, He et al[17] demonstrated that *H. pylori* induced DNA damage and replication stress in actively replicating cells. These effects occurred in *H. pylori* Cag T4SS/β-ADP-heptose/ALPK1 dependent manner, as mutants unable to assemble a competent T4SS for CagA translocation, lacking the ability to synthesize β-ADP-heptose, or lacking a serine/threonine kinase that binds β-ADP-heptose, failed to induce DNA damage and replication stress. *H. pylori* adhered to Lgr5-positive and Troy-positive stem and progenitor cells, which were the main cellular targets of *H. pylori*-mediated DNA damage. In comparison to organoids from wild-type mice, organoids from animals with inactivation of *APC* in a single allele had exacerbated DNA damage induced by *H. pylori*. *APC* inactivation significantly increased the number of actively proliferating cells, potentially expanding the pool of cells that are more susceptible to *H. pylori*-mediated DNA damage. Interestingly, recent data from Usui et al[18] evidenced that *H. pylori* modifies gastric cancer risk associated with germline pathogenic variants in homologous-recombination genes, which are involved in the repair of DNA double-strand breaks. They identified germline pathogenic variants in *CDH1* and *APC*, in mismatch-repair genes *MLH1*, *MSH2*, and *MSH6*, and in homologous-recombination genes *ATM*, *BRCA1*, *BRCA2*, and *PALB2* associated with increased risk of gastric cancer. The authors further identified an excess disease risk in participants with both a pathogenic variant and *H. pylori* infection compared to participants with either factor alone. Similar findings were obtained when the analysis was restricted to variants in homologous-recombination genes, contrasting with the lack of interaction between variants in mismatch-repair genes and *H. pylori* infection. The cumulative risk of gastric cancer at 85 years of age was 45.5% in *H. pylori*-infected carriers of a pathogenic variant in a homologous-recombination gene, compared to 14.4% in infected non-carriers and less than 5% in uninfected subjects. These findings suggest that *H. pylori*-induced DNA damage is a driver of gastric epithelial cell malignant transformation, particularly in subjects with impairment of homologous recombination.

Helicobacter pylori infection and colorectal cancer

Epidemiological evidence suggests that patients infected with *H. pylori* have an increased risk of developing colorectal cancer (CRC). A recent study by Shah et al[19] evaluated the impact of *H. pylori* infection and treatment on CRC, showing that *H. pylori* infection was associated with a small but statistically significant higher CRC incidence and mortality. Additionally, *H. pylori* eradication was associated with lower CRC incidence and mortality through a follow-up period of 15 years. Ralser et al[20] proposed that the relationship between *H. pylori* and CRC is mediated by the deregulation of intestinal immunity and induction of a mucus-degrading microbiota signature. They found that *H. pylori* infection leads to a higher tumor burden in the small intestine and colon of $Apc^{+/min}$ and $Apc^{+/1638N}$ mice compared to uninfected control animals. Infected mice had increased levels of $CD3^+$ T cells and decreased $Foxp3^+$ Treg cells, indicating a shift towards a pro-inflammatory state. *H. pylori* infection also resulted in hyperactivation of STAT3 and loss of mucus-producing goblet cells

in the intestinal epithelium, as well as in the activation of signaling pathways associated with CRC initiation and development. *H. pylori*-infected mice had enrichment of mucus-degrading bacteria such as *Akkermansia* sp. and *Ruminococcus* sp. in the colon. Eradication of *H. pylori* reduced tumor burden and decreased infiltration of $CD3^+$ T cells, normalizing STAT3 activation. Colon tissues of *H. pylori*-infected patients showed higher $CD3^+$ T cell infiltration, lower $FoxP3^+$ cell levels, increased STAT3-positive epithelial cells, and loss of mucus-producing cells compared to uninfected patients. Luo et al[21] suggested that *H. pylori* may contribute to CRC through prophage induction. In the aforementioned $Apc^{+/1638N}$ mouse model, the authors reported reduced virome diversity and richness in *H. pylori*-infected mice. Unique viral operational taxonomic units were identified in *H. pylori*-infected mice, a significant portion of which were temperate phages associated with bacteria linked to CRC development, including *Enterococcus faecalis, Ruminiclostridium*, and *Ruminococcaceae*. The authors suggest that *H. pylori* infection triggers prophage induction and has a more pronounced influence on early CRC development.

The Non-*Helicobacter pylori* Gastric Microbiome in Gastric Carcinogenesis

H. pylori is so far the only bacterium with solid evidence as a cause of gastric cancer[22]. Several studies have addressed the role of non-*H. pylori* bacteria in gastric inflammation and carcinogenesis. Lunger et al[23] evaluated the role of *Cutibacterium acnes,* a commensal that colonizes various tissues, including the gastrointestinal tract, in *H. pylori* pathogenesis. They focused on thiopeptide-producing *C. acnes*, which have antimicrobial properties and also inhibit the oncogenic transcription factor FOXM1[24]. Similarly to humans, *H. pylori*-infected male INS-GAS, and female C57BL/6 mice have increased gastric *Foxm1* expression[23]. Thiopeptide-positive *C. acnes* isolated from gastric biopsies, which inhibited *H. pylori* growth *in vitro*, was used to infect germ-free (GF) INS-GAS mice. Compared to *H. pylori*-monoinfected animals, males infected with both *H. pylori* and *C. acnes* had decreased mRNA expression of *FOXM1*, of pro-inflammatory gastric cytokines *IL1B*, *IFNG*, *TNFA*, *IL17A*, and *iNOS*, and of *FOXP3*. Coinfected male mice also had reduced gastric protein levels of the inflammatory markers IL-17, IL-10, GM-CSF, M-CSF, MCP-1, MIP-1α, MIP-2, RANTES, and VEGF, and decreased *H. pylori* colonization. These findings demonstrate the anti-inflammatory and anti-*FOXM1* properties of thiopeptide-positive *C. acnes* in *H. pylori* gastritis, but studies in longer-time courses are necessary for assessing the impact of *C. acnes* on *H. pylori*-mediated gastric cancer development.

Recent data from Fu et al[25] suggest the involvement of *Streptococcus anginosus*, which is a commensal oral species, in gastric carcinogenesis. They showed that *S. anginosus* colonization of C57BL/6 mice leads to acute gastritis at 2 weeks and chronic gastritis at 3 months post-infection. After 12 months, some of the infected animals presented gastric parietal cell atrophy, mucinous metaplasia, and low-grade dysplasia, accompanied by increased cell proliferation. In GF BALB/c mice, *S. anginosus* infection led to the appearance of mucinous metaplasia after 9 months, together with increased cell proliferation. In none of these models, *S. anginosus* infection resulted in high-grade dysplasia or carcinoma. In an N-methyl-N-nitrosourea (MNU)-induced mouse model of gastric cancer, at 9 months of MNU treatment, mice infected with *S. anginosus* had significantly higher tumor incidence and higher number of tumors in comparison to MNU-only treated mice. Mice infected with *S. anginosus* exhibited a higher incidence of high-grade dysplasia (36.4%) compared to those treated with MNU (15.4%) and were similar to the rate observed in *H. pylori*-infected mice (22.2%). Additionally, the *H. pylori*-infected group also showed a development of adenocarcinoma (5.6%). However, these findings need further validation in human studies, and the interaction between *S. anginosus* and *H. pylori* in the development of gastric cancer still needs to be clarified[26].

The Microbiome in the Gastric Tumor Microenvironment

The microbiome, both locally and at a distance, may influence the gastric tumor microenvironment by modulating inflammation, immune responses, and metabolic processes. In the local gastric microenvironment, Oosterlinck et al[27] explored how the interactions between mucins and the microbiome influence gastric cancer outcomes. Based on mucin mRNA expression, gastric tumors were classified into gastric, intestinal, mixed, or null mucin phenotypes. The intestinal mucin phenotype

and high *MUC13* mRNA expression were linked to more severe clinicopathological outcomes and worse patient survival rates. Significant differences in bacterial abundance across phenotypes were reported, with tumors with a null mucin phenotype having higher levels of *Helicobacter* and a less complex bacterial network of interactions. On the other hand, gastric tumors with intestinal and mixed phenotypes and high *MUC13* expression were linked to increased *Neisseria, Prevotella*, and *Veillonella*, and increased complexity of microbial networks. These data suggest that mucins play a role in shaping microbiome interactions in the gastric cancer microenvironment.

The gut microbiome was also shown to impact the microenvironment of gastric tumors. Yu et al[28] showed that gut microbiota-derived short-chain fatty acids (SCFA) are able to improve the immunosuppressive environment of gastric cancer. Gastric cancer patients had lower gut microbial diversity and a lower abundance of bacteria associated with SCFA production compared to healthy individuals. Decreased SCFA, such as butyric acid, was also observed in gastric cancer patient fecal samples. Fecal microbiota transplantation (FMT) from gastric cancer patients into a gastric cancer mouse model led to a higher tumor burden and decreased levels of butyric acid in mice fecal samples than did FMT from normal individuals. In gastric tumor tissues and in gastric cancer cell lines, there was a significant decrease in the expression of the butyrate receptor G protein-coupled receptor 109 (GPR109A). *In vitro*, butyrate decreased gastric cancer cell proliferation and increased cell apoptosis *via* the GPR109A/homeodomain-only protein HOPX pathway. *In vivo,* butyrate administration reduced tumor burden and increased GPR109A and HOPX levels in mice. Moreover, supplementation with butyrate or FMT from healthy donors led to elevated levels of $CD8^+$ T cells and IFNγ, while GPR109A inhibition and HOPX knockdown attenuated these effects. In agreement with these findings, Lee et al[29] showed that gut microbiome-derived butyrate inhibits immunosuppressive factors PD-L1 and IL-10 in gastric tumor-associated macrophages. The cancer mucosa of advanced gastric cancer patients had significantly higher levels of PD-L1 and IL-10 in macrophages compared to early gastric cancer patients and healthy controls. Advanced gastric cancer patients also exhibited significantly lower levels of gut butyrate-producing bacteria, including *Faecalibacterium, Collinsella, Bifidobacterium*, and *Ruminococcus*. Butyrate inhibited gastric cancer cell growth *in vitro*, decreased tumor size, and levels of PD-L1 and IL-10 and their regulators NF-KB and STAT3 *in vivo*. Altogether, these findings suggest the potential use of butyrate or of gut microbiome manipulation to reverse the gastric cancer immunosuppressive microenvironment.

The Microbiome in Gastric Cancer Immunotherapy

Influence of the gut microbiome in gastric cancer immunotherapy

Recent data has highlighted the role of the gut microbiome on the efficacy and response to cancer therapy with immune checkpoint inhibitors (ICI)[30]. Alterations to the gut microbiome can be induced by antibiotics, and antibiotic administration prior to treatment (pATB) has a negative influence on the efficacy of ICI therapies in non-small cell lung cancer (NSCLC), renal cell cancer, and melanoma. Kim et al[31] addressed the effect of pATB on gastric cancer patient outcomes after treatment with PD-1 inhibitors. pATB administration was associated with poor outcomes after anti-PD-1 treatment, including reduced response rate and decreased overall survival (OS) and progression-free survival (PFS). These results contrast with those observed in gastric cancer patients treated with the chemotherapeutic agent irinotecan, where pATB had no effect on treatment outcomes. pATB administration affected the overall composition of the gut microbiome, leading to a significant decrease in gut microbiome diversity. Patients with higher microbiome diversity or higher relative abundance of *Lactobacillus gasseri* had longer PFS and OS.

Han et al[32] studied HER2-negative advanced gastric cancer patients who received chemotherapy, ICI anti-PD-1/PD-L1 therapy, or a combined regimen. Gut microbiome analysis revealed distinct microbial profiles among the three treatment groups. The abundances of *Lactobacillus, L. mucosae*, and *L. salivarius,* were enriched in responders to ICI therapy and associated with longer PFS. In contrast, enrichment of *Streptococcus* was observed in combined therapy non-responders and was associated with reduced PFS during ICI or combined therapy. These findings, together with those of Kim et al[31], demonstrated that gut microbiota can affect the treatment response in gastric cancer patients and suggested that *Lactobacillus* may predict improved treatment efficacy.

Impact of Helicobacter pylori on gastric cancer immunotherapy

H. pylori infection has also been recently shown to have a detrimental impact on the efficacy of ICI therapy. These data stem from preclinical colorectal cancer and melanoma models but also from the analysis of patients with NSCLC or advanced melanoma undergoing anti-PD-1, or anti-PD-1 plus anti-CTLA-4 therapy, who show decreased survival when they are *H. pylori* seropositive[33,34]. To analyze the role of *H. pylori* in ICI efficacy in advanced gastric cancer, Magahis et al[35] conducted a retrospective study of 215 patients undergoing ICI treatment alone or in combination with chemotherapy, 49 of whom having history of infection with *H. pylori* documented with ^{13}C-urea breath test, stool antigen test, or histology. The PFS and OS of patients treated with ICI alone or combined therapy were significantly lower in *H. pylori*-positive patients compared to the negative patients. The PFS was even lower in *H. pylori*-positive patients receiving ICI therapy in later-line. Multivariable analysis identified *H. pylori* status as independently associated with shorter PFS and OS. Still, these findings should be interpreted with caution as there might be underdiagnosis of *H. pylori* infection due to the detection methods used[36].

Funding

PV has a fellowship from Fundação para a Ciência e a Tecnologia (FCT) with Ref. 2020.06228.BD. The team is also funded by national funds through FCT (PTDC/BTM-TEC/0367/2021).

Conflict of Interest

CF has a patent on microbiome markers for gastric cancer. The remaining authors declare no conflict of interest.

Ethics Statement

Not applicable due to the type of study.

Authors' Contributions

CF was responsible for the study's concept and design. PV and MBT reviewed individual articles to be included. PV and CF drafted the article. All authors critically reviewed the manuscript for important intellectual content and approved the final version.

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AI Statement

No artificial intelligence has been used for this article.

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