

REVIEW

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Interplay and cooperation of *Helicobacter pylori* and gut microbiota in gastric carcinogenesis

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Abstract

Chronic *Helicobacter pylori* infection is a critical risk factor for gastric cancer (GC). However, only 1–3 % of people with *H. pylori* develop GC. In gastric carcinogenesis, non-*H. pylori* bacteria in the stomach might interact with *H. pylori*. Bacterial dysbiosis in the stomach can strengthen gastric neoplasia development via generating tumor-promoting metabolites, DNA damaging, suppressing antitumor immunity, and activating oncogenic signaling pathways. Other bacterial species may generate short-chain fatty acids like butyrate that may inhibit carcinogenesis and inflammation in the human stomach. The present article aimed at providing a comprehensive overview of the effects of gut microbiota and *H. pylori* on the development of GC. Next, the potential mechanisms of intestinal microbiota were discussed in gastric carcinogenesis. We also disserted the complicated interactions between *H. pylori*, intestinal microbiota, and host in gastric carcinogenesis, thus helping us to design new strategies for preventing, diagnosing, and treating GC.

Keywords: *H. pylori*, gut microbiota, interaction, gastric carcinogenesis

Background

Helicobacter pylori infection is the critical risk factor for gastric cancer (GC) [1–4]. Inflammation and injury induced by *H. pylori* can continuously damage the function and architecture of the gastric epithelium [5]. However, it should be mentioned that the successful removal of *H. pylori* does not necessarily inhibit the GC development [6]. Thus, there may be other factors involved in the carcinogenesis of GC which require further research. Numerous intestinal and gastric microbes have been known as procarcinogens in colorectal cancer and GC [7–11], or probiotics that increase patients' immunotherapy response with cancer [12]. However, there are few reports about microbiota composition in precancerous lesions.

Normal intestinal flora (IF) has been indicated to accelerate the beginning of gastrointestinal intraepithelial neoplasia (GIN) and increase its development [13]. Non-*H. pylori* bacteria, pathogenic or commensal IF, may colonize the stomach and show the excessive risk of gastric adenocarcinoma, especially in susceptible patients with *H. pylori* [14, 15]. INS-GAS (insulin-gastrin) transgenic mice with high levels of circulating gastrin develop spontaneous atrophic gastritis and GIN with an 80 % prevalence 6 months after *H. pylori* infection. Evaluation of this model revealed that commensal intestinal bacteria may promote GC. [16, 17]. Male restricted ASF (a restricted microbiota confined to three species of Altered Schaedler's Flora) and IF INS-GAS mice presented gastric pathology as the Correa model, even without *H. pylori* infection [18]. Although ASFs are beneficial for mice [19], it appears that their colonization in the stomach may be involved in the production of various oxidizing agents, oxygen radicals, nitrosamines, and genotoxic

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compounds and mutagens. Various studies have shown that human gastric colonization with bacteria other than *H. pylori* such as *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, *Firmicutes*, and *Bacteroides* (many are colonized normally in the lower intestine) can affect the gastric adenocarcinoma risk [17, 20–22]. *Lactobacillus* is a facultative anaerobe representing a gut microbiota component and is in general a probiotic in-transit passenger. The gastric mucosa colonization by *Lactobacillus* shows an alteration in cancerous patients with gastric microenvironment. A study in Taiwan showed that *Lactobacillus* is abundantly found in GC patients. This seems to be due to the use of probiotic microbes as a dietary supplement [23].

Gastritis can change the fecal microbiome composition, which might possibly be aggravated by *H. pylori* infection [24]. The gut microbiome changes could be associated with chronic gastrointestinal diseases, the close interaction of *H. pylori* infection, gut microbiome, and gastritis [24]. Numerous pieces of evidence show that bacteria and host response interplay may form commensal microbiota composition though the precise mechanism of gastric inflammation leading to fecal microbiota variations is not indicated properly. Gastric microbiota and luminal pH changes may drive the community structure of gut microbiota [25].

Previous studies stated that colonization with non-*H. pylori* bacteria, gut commensals, changes the ‘resident’ gastric microbiota and the host equilibrium [11]. This article mainly reviewed the influence of intestinal microbiota on GC. Next, it discussed the potential mechanisms of intestinal microbiota in carcinogenesis. Moreover, the interactions between *H. pylori*, intestinal microbiota, and host in cancer induction were disserted. In the last part of this review, the effects of *H. pylori* and gut microbiota on metabolic pathways were discussed.

Main text

Gut microbiota in GC

Lactobacillus, *Lachnospiraceae*, *Escherichia-Shigella*, *Nitrospirae*, and *Burkholderia* are enhanced in GC patients compared with controls [8], confirming previous results with respect to the fact that *Lachnospiraceae* and *Lactobacillus* are abundantly found in GC [15, 26–28]. The findings pose a hypothesis; gastric colonization through non-*H. pylori* bacteria affects the GC risk, and many of them also colonize the intestine. The study by Ferreira et al. approved a notable decline in the abundance of *Helicobacter* and a significant increase in the genera *Achromobacter*, *Clostridium*, *Citrobacter*, *Rhodococcus*, and *Lactobacillus* in Portuguese patients with GC in comparison with chronic gastritis, the ORs were 20.5 (95 % CI 7.4–59), 5.7 (95 % CI 2.2–15), 9.9 (95 % CI 4.3–23), 4.2 (95 % CI 1.7–11), and 6.3 (95 % CI 2.9–14),

respectively [11]. These members of microbiota are present as commensals in the intestinal mucosa but might be opportunistic pathogens [29, 30]. Evaluations on gastric microbiota show that *Lactobacillus* is highly abundant in progressive histological phases of gastric carcinogenesis and in GC patients [8, 10, 11, 26]. A study in Sweden found that *Lactobacillus* was one of the predominant genera in GC patients [15]. Increase of *Lactobacillus* sp from non-atrophic gastritis, to intestinal metaplasia and to GC was characterized in Mexican patients’ stomach microbiota using the microarray G3 PhyloChip [26]. In another study from Taiwan, *Lactobacillus* was a highly abundant species in GC patients [23]. Some commensal bacteria were overrepresented in GC. A large amount of *Klebsiella pneumoniae* and *Escherichia-Shigella* (belonging to *Enterobacteriaceae* taxa) was detected in GC patients’ gastric mucosa [7, 8]. A study in China showed that the dominant phyla in the feces of patients with gastric lesions were *Firmicutes*, *Bacteroidetes*, and *Proteobacteria* that accounted for the 99.05 % of all fecal bacteria, and *Bacteroides*, *Escherichia-Shigella*, *Prevotella_9*, and *Ruminococcus_2* were the predominant genera [31]. Another study showed that there existed 12 bacterial genera enriched in GC, involving *Prevotella_9*, *Klebsiella*, *Lactobacillus*, *Escherichia-Shigella*, *Streptococcus*, *Veillonella*, *Alistipes*, *Bifidobacterium*, *Christensenellaceae_R-7_group*, *Ruminococcaceae_UCG - 002*, *Prevotella_2*, and *Parabacteroides*. *Enterobacteriaceae* and *Lachnospiraceae* had to be considered at the family level [32]. *Veillonella*, *Lactobacillus*, and *Streptococcus* of GC were increased, in terms of relative abundance, by 32.38-fold, 58.92-fold, and 15.93-fold, and *Tyzzereella_3* and *Lachnospira* were declined by 8.85-fold and 3.37-fold, respectively. These reports show that the genera *Lactobacillus*, *Streptococcus*, *Veillonella*, *Tyzzereella_3*, and *Lachnospira* were employed to predict GC [32]. A study in China has shown that some *Actinobacteria* and *Firmicutes* species were considerably decreased in patients’ feces with esophageal cancer or GC compared to healthy individuals ($P < 0.05$) (Table 1) [33]. In comparison with normal and peritumoral tissues, *Prevotella copri* and *Bacteroides uniformis* showed a reduction while *Propionibacterium acnes*, *Streptococcus anginosus*, and *Prevotella melaninogenica* experienced an enhancement in tumor tissues [34]. Based on a recent study on various GC subtypes, *Patescibacteria*, *Bacteroidetes*, and *Fusobacteria* were enhanced in signet-ring cell carcinoma, while *Acidobacteria* and *Proteobacteria* showed an incremental trend in adenocarcinoma [35].

Potential mechanisms of gut microbiota in carcinogenesis

Gut microbiota mechanisms contributing to carcinogenesis are not clear yet. Dysbiotic microbial community may increase the risk for gastric carcinoma by sustaining

Table 1 The relationships of Gut microbiota with GC in the world

Gut microbiota (genera/species)	Related to increase ↑/decrease ↓ of GC	Country	ASR-Both sexes (GLOBOCAN 2018)	Study (Reference)
<i>Lactobacillus</i> , <i>Lachnospiraceae</i> , <i>Escherichia-Shigella</i> , <i>Nitrospirae</i> , and <i>Burkholderia</i>	↑	China	20.7	Wang et al., 2016 [8]
<i>Lactobacillus</i> and <i>Lachnospiraceae</i>	↑	South Korea	39.6	Eun et al., 2014 [28]
genera <i>Achromobacter</i> , <i>Clostridium</i> , <i>Citrobacter</i> , <i>Rhodococcus</i> , and <i>Lactobacillus</i>	↑	Portugal	11.0	Ferreira et al., 2018 [11]
<i>Lactobacillus</i>	↑	China	20.7	Coker et al., 2018 [10]
genera <i>Streptococcus</i> , <i>Lactobacillus</i> , <i>Veillonella</i> , and <i>Prevotella</i>	↑	Sweden	3.3	Dicksved et al., 2009 [15]
<i>Lactobacillus</i> sp. and <i>Lachnospiraceae</i>	↑	Mexico City	5.6	Aviles-Jimenez et al., 2018 [26]
<i>Lactobacillus</i>	↑	Taiwan	-	Hsieh et al., 2018 [23]
<i>Escherichia-Shigella</i> and <i>Klebsiella pneumoniae</i> (belonging to Enterobacteriaceae taxa)	↑	South Korea	39.6	Jo et al., 2016 [7]
12 bacterial genera, including <i>Prevotella_9</i> , <i>Escherichia-Shigella</i> , <i>Klebsiella</i> , <i>Lactobacillus</i> , <i>Streptococcus</i> , <i>Alistipes</i> , <i>Veillonella</i> , <i>Bifidobacterium</i> , <i>Ruminococcaceae_UCG-002</i> , <i>Christensenellaceae_R-7_group</i> , <i>Parabacteroides</i> , and <i>Prevotella_2</i>	↑	China	20.7	Qi et al., 2019 [32]
Species of <i>Firmicutes</i> and <i>Actinobacteria</i>	↓	China	20.7	Li et al., 2019 [33]

the gastric inflammatory process and triggering immune responses [11]. Also, microbial dysbiosis can increase inflammation and dysregulate the immune response, causing DNA mutations, hence, hastening the induction and/or progression of cancers. Such a mechanism may be due to interactions between fecal microbiota, *H. pylori* infection, and host responses [31]. It is well known that gastritis activity is correlated with *H. pylori* infection. Subsequent studies also confirmed such an association between gastritis activity and fecal microbiota. Intestinal flora could also increase the inflammatory responses in the mice stomach infected by *H. pylori*, promoting the development of neoplasia and gastric atrophy [36].

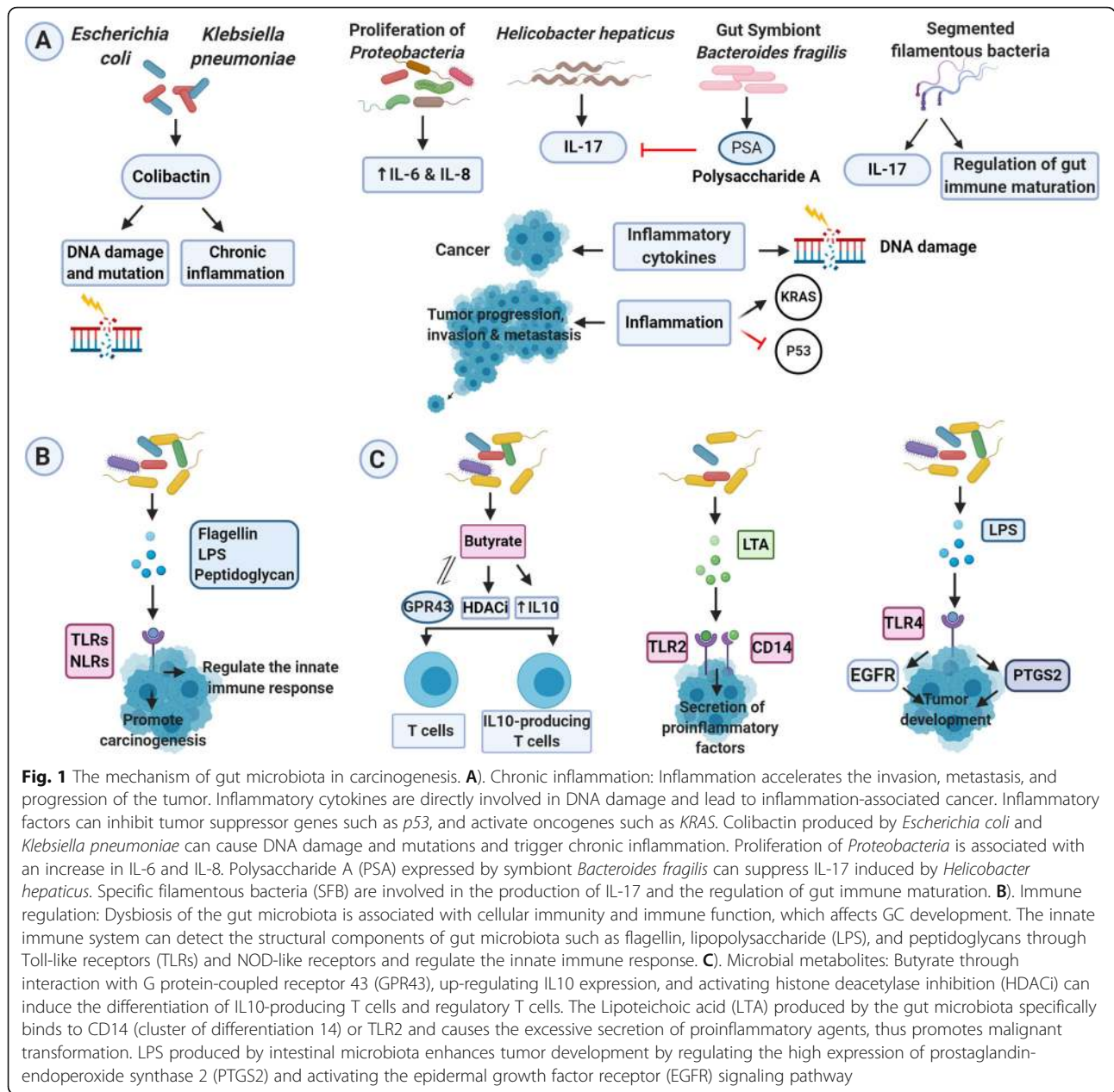
Chronic inflammation

Inflammation aggravates the progression of tumor and hastens metastasis and invasion. Inflammatory cytokines damage DNA in the epithelium directly and induce inflammation-associated cancers [37]. The inflammation associated factors can stimulate oncogenes (e.g., *KRAS* mutation) and inactivate tumor-suppressor genes (e.g. *p53* mutation) [38, 39]. Investigations show that there exists an association between detrimental alterations in the composition of fecal microbiota and the increase in proinflammatory cytokines that induces the disease. *K.*

pneumoniae and Colibactin-producing *Escherichia coli* can cause chronic inflammation, DNA damage, and mutation [40, 41]. Biagi et al. correlated the *Firmicutes* and *Bacteroidetes* reduction and *Proteobacteria* proliferation with IL-6 and IL-8 increases [42]. IL-11 and IL-6 can sensitize signal transducer and activator of transcription 3 (STAT3) activator, exerting a considerable effect on epithelial cells' transformation [43]. The symbiont *Bacteroides fragilis*, which expresses polysaccharide A, is able to suppress proinflammatory IL-17 generation which is developed via *Helicobacter hepaticus* [44]. Intestinal commensals, segmented filamentous bacteria (SFB) in particular, were correlated with the gut immune maturation regulation and IL-17 generation (Fig. 1A). [45]. Lipoteichoic acid (LTA) also binds to CD14 or Toll-like receptor 2 (TLR2), inducing the excessive secretion of proinflammatory factors [46, 47].

Microbial metabolites

Intestinal microbial dysbiosis has been associated with cellular immunity and immune function, which affects the GC development [48, 49]. NOD-like receptors (NLRs) and TLRs [50] can bridge this interplay, eventually promoting carcinogenesis in a chronic process. TLRs critically affect the innate immune system, assuming their capability in differentiating host molecules from



microbial molecules. NLRs adjust the innate immune response, correspondingly activating inflammasome-mediated dysbiosis and modulating microbial composition (Fig. 1B). The gut microbiota can generate butyrate, which can differentiate regulatory T cells and IL10, generating T cells via the activation of histone deacetylase inhibition (HDACi), interactions with G protein-coupled receptor 43 (GPR43), and IL10 up-regulation [51]. LTA and short chain fatty acids (SCFAs) have opposite roles in carcinogenesis [52]. LTA accelerates malignant transformation. In contrast, SCFAs can mediate immunoregulation by Tregs, hence showing anti-carcinogenic and

anti-inflammatory effects [51, 53, 54]. TLRs can develop gastrointestinal tract tumors by activating the STAT3 and NFKB signaling pathways [50]. The TLR4 activation, the receptor for LPS generated by the gut microbiome in the epithelial cells, can induce tumor development by up-regulating prostaglandin-endoperoxide synthase 2 (PTGS2) and activating the epidermal growth factor receptor (EGFR) signaling pathway in mice receiving AOM (Fig. 1C) [55]. In addition, the activation of the STAT3 signaling pathway up-regulates the expression of TLR2 in gastric epithelial cells, promoting tumor development in mice stomach [56].

Bacterial genotoxins

It has been shown that intestinal bacteria are able to potentiate carcinogenesis by the specific toxins inducing DNA damage. As the disturbed microbes overgrow, they increase accumulating endotoxins and exotoxins, like cytolethal distending toxin from *Shigella dysenteriae*, cytolethal distending toxin and colibactin from *E. coli*, hydrogen peroxide, extracellular superoxide from *Enterococcus faecalis*, Enterotoxigenic *B. fragilis* toxin, a virulence factor activating the NF- κ B and WNT signaling pathways in epithelial cells [57–59], from *B. fragilis*, etc. These toxins directly or indirectly cause genomic instability, DNA damage, and the invasion of adenocarcinomas [40, 60–62]. Colibactin in *E. coli* can induce DNA damage, influence genomic instability [40, 63], and promote carcinogenesis. Colibactin-producing *K. pneumoniae* can induce chronic inflammation, DNA damage, and mutation [41]. Cytolethal distending toxin produced by the *Helicobacter* species and *E. coli* can induce DNA damage in mammalian cells [64–67]. The accumulation of base excision repair (BER) intermediates and unrepaired DNA cause genomic instability and carcinogenesis [68, 69].

Mechanism of *H. pylori* in carcinogenesis

Genetic diversity can be defined as a leading characteristic of *H. pylori* strains due to intra-/intergenomic recombination and point mutations [70] which is correlated with the *H. pylori* pathogenicity, affecting the risk of malignancy [71]. *H. pylori* can regulate many signaling pathways, stimulate inflammation and immune responses, and trigger epithelial atrophy, achlorhydria, and dysplasia cancer [72]. *H. pylori* infection induces both innate and adaptive immune responses [73]. Upon recognition of *H. pylori* pathogen-associated molecular patterns (PAMPs) by the pattern recognition receptors (PRRs) of host cells, the initial stages of the innate immune responses are triggered [74]. As the main component of PRRs, TLRs have the ability to bind the LPS, CpG repeats, unmethylated nucleic acids, flagellin, double-stranded RNA, lipoteichoic acid, and lipoproteins of *H. pylori* [75]. Upon recognition of PAMPs, by activating activator protein (AP)-1, interferon regulatory factor (IRF), and NF- κ B, TLRs manage to promote the expression of inflammatory mediators like TNF- α , IL-1, IL-2, IL-6, IL-8, IL-12, and IFN- γ [76, 77]. *H. pylori* is able to escape the recognition by the host PRRs of the innate immune response, which may lead to its long-term survival [78]. Concerning adaptive immunity, CD4⁺ T cells mediate the host immune response toward *H. pylori* infection [79]. CD4⁺ T cells have a higher abundance in GC samples than the peritumoral and normal tissues, while CD8⁺ T cells exhibited the opposite trend [80].

Inflammatory cytokines are highly accumulated in *H. pylori*-infected individuals' stomach, including interferon- γ , IL-1, TNF- α , IL1b, IL-7, IL-6, IL-8, IL-18, and IL-10. The oncogenic pathways' activity containing ERK/MAPK, NF- κ B, sonic hedgehog, PI3K/Akt, Ras, Wnt/beta-catenin, and STAT3 is up-regulated with *H. pylori* carrying cytotoxin-associated gene A (CagA). In contrast, with induced P53 mutations, tumor suppressor pathways become inactivate [81, 82]. *H. pylori* infection can induce methylations on E-cadherin CpG islands [83] and tumor-suppressor genes, consisting of those which encode a forkhead box transcriptional regulator (FOXO3) and the trefoil factor 2 (TFF2), which markedly increase the adenocarcinoma risk in the stomach [84]. The oncoprotein CagA and vacuolating cytotoxin A (VacA) are critical pathogenic factors of *H. pylori* infection [1, 85–87]. *H. pylori* expresses the CagA protein, which is a virulence factor that promotes cell proliferation by the activation of the signaling pathways of WNT, PI3K-AKT, and NF- κ B [88–90], and reduces epithelial cell apoptosis by inhibiting TP53 [91]. Also, CagA has been approved to activate stemness features and stimulate the epithelial-mesenchymal transition (EMT) in gastric cells [92–96]. By acting on gastric epithelial cells, CagA promotes carcinogenesis through inflammation, proliferation induction, apoptosis inhibition, cell-cell bonding disruption, and loss of cell polarity [97]. The VacA toxin suppresses host immunity via inhibiting the activation of T-cells and inducing regulatory T cells [98–101]. The host immune response can be also modulated by VacA through inhibition of immune cell proliferation and stimulation of mast cells to produce proinflammatory cytokines; further promoting the development of gastritis associated with *H. pylori*, peptic ulceration, and GC [102]. It induces cell vacuolation [87, 103–105] and autophagy in human-derived gastric epithelial cells [106, 107] through directly affecting mitochondria [108–110], activating vascular endothelial growth factor [111, 112], up-regulating MAP kinase and ERK1/2 expression [113], up-regulating Wnt/beta-catenin pathway necessary for cell differentiation and growth [114], and suppressing GSK3 by the PI3K/Akt signaling pathway [115].

H. pylori virulence factors are involved in the host immune response [79]. The release of inflammatory mediators can activate Th1/Th17 cell responses and stimulate the production of TNF- α , IL-17, and IFN- γ [116]. Therefore, Th1/Th17 cells contribute to mediating the inflammatory response of patients suffering from *H. pylori* infection [116]. Inflammation may result in loss of acid-secreting parietal cells, hence, increasing the stomach pH, giving rise to declined *H. pylori* levels and incremental colonization of other bacteria [117]. *H. pylori* and chronic inflammation can promote the generation of

both reactive nitrogen species (RNS) and reactive oxygen species (ROS), leading to DNA damages and induction of apoptosis or autophagy in the gastric epithelial cells [118]. Therefore, *H. pylori* can induce gastric carcinogenesis through genetic instability. Moreover, ROS induces DNA mutations in *H. pylori*, promoting its adaption to the host environments [119]. *H. pylori*-derived LPS can also cause specific impacts on GC cells through TLR4. *H. pylori* LPS stimulation activates the TLR4 signaling pathway in GC cells through affecting the expression of soluble factors or surface molecules which might help their evasion from CTLs or NK cells by IFN- γ -mediated cellular immune reaction [120]. Low induction of cellular immune response by *H. pylori* LPS can promote the host susceptibility toward GC development [120]. Based on Kidd et al., *H. pylori* LPS showed a specific mitogenic influence on gastric enterochromaffin-like cell neoplasia. LPS may exhibit poor virulence in evoking an inflammatory response while showing high potential in augmenting cell growth [121]. The enhanced LPS biosynthesis pathway of GC samples promoted microbiota-induced inflammations [122, 123].

Interplays between *H. pylori* and gut microbiota

H. pylori infection can affect gut microbiota [122, 124]. It is associated with altered gastric microbiota and dysbiosis implicated in gastric disease pathogenesis [10, 11]. Wang et al.'s study showed that *H. pylori* infection was related with variations in human intestinal microbial composition and function in Chinese people [125]. Colonization of the stomach with IF (intestinal flora) promotes *H. pylori*-associated GC. IF effect in developing GC during *H. pylori* infection has been confirmed in previous studies [36]. Some bacteria, including *Bacteroides*, *Clostridium histolyticum*, *Prevotella* spp., and *Lactobacilli* have been associated with *H. pylori* infection in animal models and human trials [126–128]. *Prevotella copri* is known as a gut microbe that plays a role in the immune system. It was enriched significantly in *H. pylori*-positive patients. The continuous *H. pylori* colonization in the stomach brings about the host immune response [128, 129]. A study on a high-risk population showed that the genera *Gemella*, *Rhodococcus*, *Acidovorax*, and *Erysipelotrichaceae*_UCG-004 in fecal samples were associated with current *H. pylori* infection [31]. The relative abundances of dominant phyla in the gut of patients with positive *H. pylori* infection, involving *Firmicutes*, *Bacteroidetes*, and *Proteobacteria* are markedly different from those of individuals with negative *H. pylori* infection and may be associated with gastric lesions. The average relative abundances, for *Proteobacteria* and *Firmicutes*, showed high trends in the past *H. pylori* infection group (47.11, 20.53%) in comparison

with the negative group (23.44 and 9.05%, respectively) although the *p*-values (0.068 and 0.246, respectively) revealed no meaningful variations [31]. A study on 1,123 Japanese adults approved more *Lactobacillus* in patients with *H. pylori*-infected patients suffering from severe atrophic gastritis [130]. According to Iino et al., infection with *H. pylori* initially affected the *Lactobacillus* species' composition ratio in the gut microbiota prior to the progression of atrophic gastritis and proposed a greater *Lactobacillus* abundance in patients with *H. pylori* who suffered from severe atrophic gastritis [130]. Based on a German study, *H. pylori* increased the *lactobacilli* growth in fecal microbiome [126]. In the study by Yang et al., fecal microbiome was investigated in children with *H. pylori*-positive/-negative gastritis and healthy control groups. It was shown that at family and genus levels, the relative abundances of *Enterobacteriaceae* and *Bacteroidaceae* were common in gastritis with and without *H. pylori* infection, while the relative abundances of *Lactobacillaceae*, *Bifidobacteriaceae*, and *Lachnospiraceae* were high in healthy control group. To evaluate the *H. pylori* effect on gut microbiome among children, the fecal microbiome was analyzed in *H. pylori*-positive and -negative gastritis groups. The higher abundance of *Lactobacillales* and *Betaproteobacteria* and the lower abundance of *Alphaproteobacteria* were observed in *H. pylori*-positive group. Higher *Streptococcus* and *Collinsella* abundance was found at the genus and family levels in *H. pylori*-positive group relative to *H. pylori*-negative group [24]. The *H. pylori*-infected children also showed increased the number of gut microbiota including *Firmicutes*, *Proteobacteria*, *Prevotella*, and *Clostridium* compared with those without the infection [131]. In a study by Maldonado-Contreras, microbial community in *H. pylori*-positive subjects indicated an increase in the counts of *Proteobacteria*, *Acidobacteria*, and *Spirochaetes* [17]. In another study, the gut microbiota of individuals infected with *H. pylori* was reported to elevate in members of *Succinivibrio*, *Enterococcaceae*, *Coriobacteriaceae*, and *Rikenellaceae*. The greater abundance of these genera in individuals with *H. pylori* infection may be associated with the early stages of cancer development and *H. pylori* pathogenesis [132].

Various studies have shown that *H. pylori* infection affects the structure of the gut microbiota population. In contrast, some have reported that gut microbiota affects *H. pylori* colonization. As the diversity of intestinal flora microbiota increases, the level of *H. pylori* colonization decreases [36]. *H. pylori* eradication also incremented microbial diversity of the stomach [133]. Study of subjects at different gastric carcinogenesis histologic stages (gastritis, intestinal metaplasia, and GC) showed an inverse association between *H. pylori* load and microbial diversity of non-cancer gastric biopsies, whereas GC

showed a lower diversity in comparison with other samples having the same *H. pylori* abundance; the difference could be assigned to antibiotic treatment [133]. *Lactobacillus casei* has been reported to inhibit the growth and colonization of *H. pylori* in the stomach [134]. Other studies have proved contradictory results about *Lactobacillus*. A study on *H. pylori* and *Lactobacillus* coisolates from humans did not prove a significant effect of *lactobacilli* on *H. pylori* strains [135]. A study on the gut microbiota of children with negative *H. pylori* showed the higher relative abundance of *bacteroidia*, *gammaproteobacteria*, *clostridia*, and *betaproteobacteria*, and a greater bacterial diversity and richness [136]. A study in China on children's stool samples showed that at the genus and family levels, the lower abundances of *Erysipelotrichaceae*, *Pseudomonadaceae*, and *Megasphaera* were seen in *H. pylori*-positive group relative to *H. pylori*-negative group. It was also shown that the frequency of *Faecalibacterium* and *Roseburia* in the *H. pylori*-positive group was reduced compared to the healthy control group [24]. Many groups have employed sequencing-based and PCR-based methods to show that individuals with negative *H. pylori* have a very diverse gastric microbiota that is dominated by five predominant phyla: *Proteobacteria*, *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, and *Fusobacteria* [16, 17, 137]. Conversely, *H. pylori* is the utmost abundant bacterium in the stomach and involves the 97 and 72 % of all sequence reads among the subjects with positive *H. pylori* [16, 137]. In a study by Maldonado-Contreras, the microbial community in individuals with positive *H. pylori* was known by a decline in *Bacteroidetes*, *Actinobacteria*, and *Firmicutes* counts [17]. Bik et al., reported that the individuals with negative *H. pylori* carry the higher abundant phyla of *Bacteroidetes*, *Firmicutes*, and *Actinobacteria* [16]. Conversely, a study from China showed that the relative abundance of *Bacteroidetes* was greatly reduced from *H. pylori* negative to past infection community (66.16 %, 33.01 %, respectively; $p = 0.007$). *Rhodococcus* and *Acidovorax* had slightly lower average relative abundance at the genus level in patients that are currently infected with *H. pylori* compared with others that are not currently infected ($p = 0.017$ and 0.016 , respectively). It was also shown that the average relative abundance of the two genera (the phylum of *Bacteroidetes*; *Barnesiella* and *Parabacteroides*) was decreased among the groups having the different status of *H. pylori* infection (negative: 1.15 and 2.44 %, past infection: 0.58 and 1.27 %, respectively) [31].

***H. pylori* and gut microbiota interaction in cancer**

The interactive associations between *H. pylori* and other gastric bacteria have not been completely understood [102]. *H. pylori* infection has been linked to altered

gastrointestinal microbiota and dysbiosis, all of which have been linked to the pathogenesis of gastric diseases [10, 11]. It is not, however, clear whether infection with *H. pylori* itself approves the growth of unwanted microorganisms or an altered microbiota brings about beneficial situations for the colonization of *H. pylori* [123]. Probably, there is a multifaceted interaction, where the *H. pylori* colonization contributes to the growth of some microbes and vice versa. It is likely that dysbiosis alters gastric mucosa which is highly desired for the colonization of *H. pylori* [124].

Some researchers believe that *H. pylori* is more of a latent or opportunistic pathogen than a pathogenic bacterium and can be considered a commensal organism. This is important because we know that the majority of the world's population is infected with *H. pylori* and colonization occurs with bacteria that carry or do not carry critical virulence factors at an early age. However, it should be noted that severe gastrointestinal diseases or complications occur mainly in adults with age > 40 years and only in < 10 % of infected individuals. This low incidence clearly showed that *H. pylori* is more of a latent or opportunistic pathogen than a pathogenic bacterium, and that virulence factors play little role in the outcome of the disease [138]. Long-term colonization of *H. pylori* and its interaction with other gastric microbiota appear to alter gastric mucosal dysbiosis and lead to the development of severe gastrointestinal disease, including GC, by inducing persistent and long-term inflammatory responses [31, 124].

It can be speculated that the alterations of gut microbiota induced by *H. pylori* may affect the development of GC since the composition of microbiota stimulates immune responses at a systemic and local level; moreover, the development of GC is affected by inflammatory signaling [31]. The interaction between gut microbiota and *H. pylori* is not known yet and literature reveals inconsistent results [132]. The gastritis activity is perceived for its tight correlation with *H. pylori* infection, which is further approved by similar changes observed in the fecal microbiota from the subjects with non-active gastritis and past infection. Additionally, the same alteration tendencies were found for major genera or phyla, including reduced *Bacteroidetes* abundance and increased *Proteobacteria* or *Firmicutes* abundances, with gastric lesion severity and *H. pylori* infection status (particularly the status of past infection). Furthermore, it states that changes in intestinal microbiota may develop precancerous gastric lesions related to *H. pylori* and carcinogenesis [31]. It has been suggested that lactic acid-producing bacteria may promote gastric inflammatory reactions induced by *H. pylori* [24]. Lactic acid bacteria promote immune tolerance, providing the platform for colonization of other carcinogenic bacteria [139].

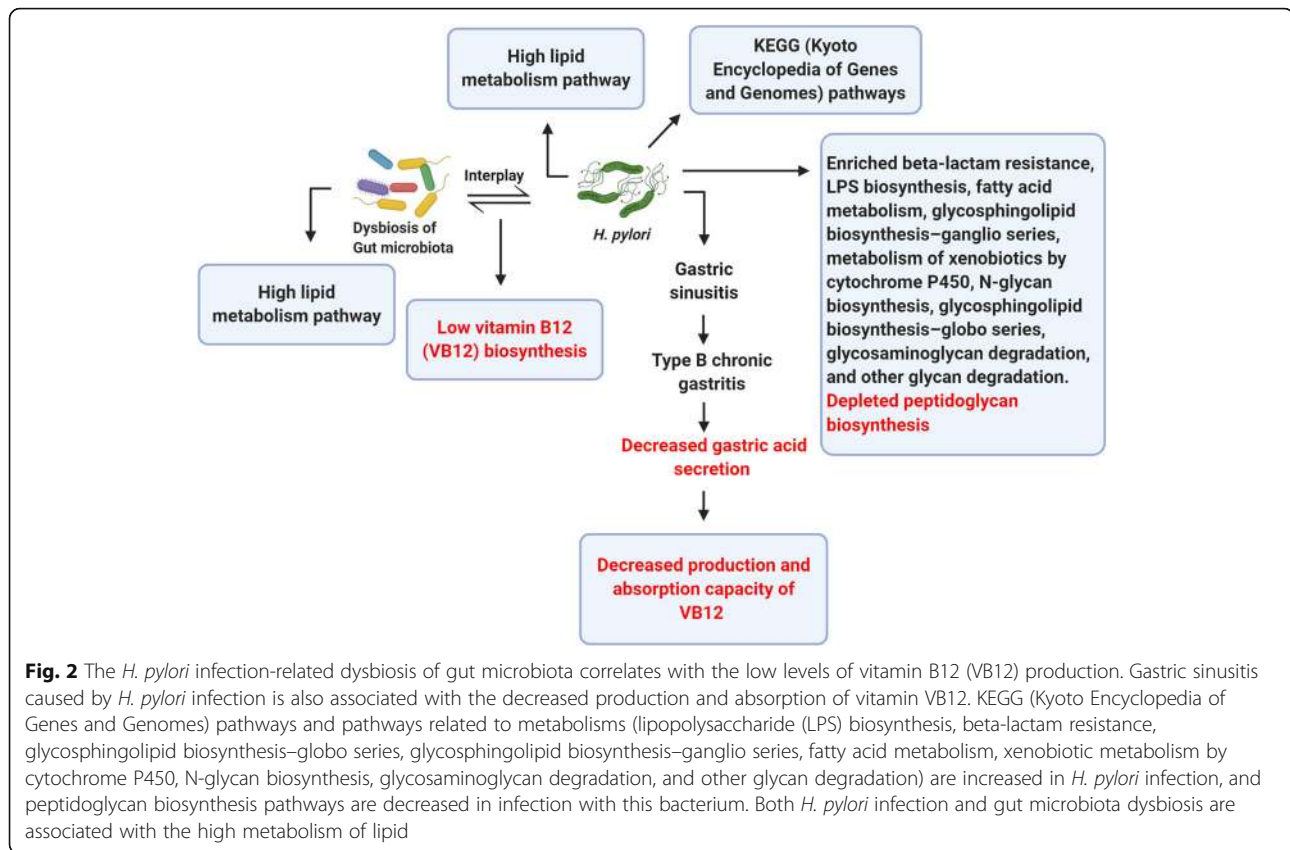
By modulating the acidity of the stomach, *H. pylori* could change the gastric microbiome profiles, promoting *H. pylori*-associated disorders. Alterations in the gastric environment that decline acid secretion can encourage the growth of NOC-producing bacteria, thus elevating the chance of gastric carcinogenesis [102]. Th1/Th17 cells contribute to the inflammatory response of *H. pylori*-infected patients [116, 140]. Inflammation increases gastric pH, which decreases *H. pylori* levels and increases non-*H. pylori* bacteria in the stomach [117]. There is a significant difference in the microbial profiles and composition of early and advanced GC, reflecting the changes related to GC progression. The gastric microbiome alterations in early GC stages could be assigned to host genetic changes, *H. pylori* infection, bacterial virulence, and adaptation to the environment. Constrained principal coordinate analyses indicated the influence of *H. pylori* and *cagA* and *vacA* genotypes on the gastric microbiome structure. The detected microbial fingerprint can be regarded as a biomarker for clinical evaluation of GC risk among high-risk cases [141].

Effect of *H. pylori* and gut microbiota on metabolic pathways and carcinogenesis

Gut microbiota changes correlate with different inflammatory and metabolic illnesses. Little is known about the effect of *H. pylori* on downstream gut microbiota though many studies have examined the correlation between gastric microbiota and *H. pylori* [132]. Microbiome alterations are often followed by variations in microbial functions. The relative abundance of 19 gut microbial pathways differs significantly between *H. pylori*-negative and *H. pylori*-positive subjects [142]. Persistent *H. pylori* infection can induce detrimental inflammatory processes besides the impact on host microbes [143]. Epidemiological studies show that *H. pylori* infection is related with the lower levels of vitamin B12 (VB12) in the blood [144, 145]. The *H. pylori* infection-related intestinal microbiota dysbiosis can influence the VB12 production. VB12 is a cobalt corrinoid. As humans cannot produce VB12, it is generated exclusively by the microorganisms, especially anaerobes [146]. In the study of Wang et al., it was observed that the levels of plasma VB12 and gut microbial VB12 biosynthesis were meaningfully lower in the subjects with positive *H. pylori* in comparison to the subjects with negative *H. pylori* ($p < 0.05$, Wilcoxon test). Lower VB12 biosynthesis module was linked to the lower levels of VB12 concentrations in subjects with *H. pylori* infection, manifesting that *H. pylori* infection-related gut microbiota dysbiosis enhances the VB12 deficiency risk. This shows that some changes in gut microbial species and functions correlate with *H. pylori* infection, suggesting that the gut microbial shift in the patients with *H. pylori* infection may raise VB12

deficiency indirectly [125]. In addition, previous studies have inferred that gastric sinusitis, induced by *H. pylori* infection, may develop type B chronic gastritis, followed by reduced the secretion of gastric acid, leading to VB12 malabsorption [145, 147]. Thus, both the absorption capacity and production of VB12 can be attenuated by *H. pylori* infection, augmenting the VB12 deficiency risk. Low serum vitamin B12 levels are significantly correlated to the elevated risk of non-cardia gastric adenocarcinoma (NCGA) [148]. *H. pylori* infection has been also related to food-bound vitamin B12 malabsorption [149, 150] possibly because of the atrophic gastritis induction which is accompanied by achlorhydria (increased gastric pH). Furthermore, vitamin B12 absorption needs acid-producing gastric mucosa, allowing for vitamin B12 cleavage from its binding proteins [151]. As a result, any stimulus inducing chronic atrophic gastritis can enhance the risk of NCGA, disturb vitamin B12 absorption, and thus, declines its serum concentrations [148]. Since vitamin B12 uptake necessitates intact gastric mucosa for acid production, the findings proposed vitamin B12 as a potential serologic marker of NCGA-preceding atrophic gastritis [148].

A recent study on children has shown that altered intestinal microbiota, gastritis, and *H. pylori* interact with each other. Possibly, *H. pylori* changes the gut micro-environmental cues, like pH alterations that cause this compositional shift between native communities to compensate. This compensation will be translated into distinctive functional genes contributing to crucial metabolic pathways [132]. It has also been shown that gut microbiome influenced by gastritis and *H. pylori* infection changes the body's basal metabolic function [24]. Seventeen KEGG pathways revealed notable variations in *H. pylori*-infected group and healthy control group. The results of this study manifested the meaningful increase of activity in children's metabolic pathways, who are *H. pylori*-positive [24]. However, peptidoglycan biosynthesis was depleted in the *H. pylori*-positive group as metabolism-related pathways (fatty acid metabolism, LPS biosynthesis, beta-lactam resistance, xenobiotics metabolism by cytochrome P450, glycosphingolipid biosynthesis–ganglio series, glycosphingolipid biosynthesis–globo series, N-glycan biosynthesis, and glycosaminoglycan degradation) were enriched in the *H. pylori*-positive group [24]. *H. pylori* is dependent on unsaturated fatty acid (UFA) biosynthesis to maintain its membrane function and structure [152]. The microbial UFA level is meaningfully increased in the blood of the patients developing *H. pylori*-induced peptic ulceration [153]. Based on these results, it can be said that *H. pylori* is associated with the high metabolism of lipid. According to the microbiome's functional analysis, lipid metabolism pathway was increased in the gastritis group, showing that



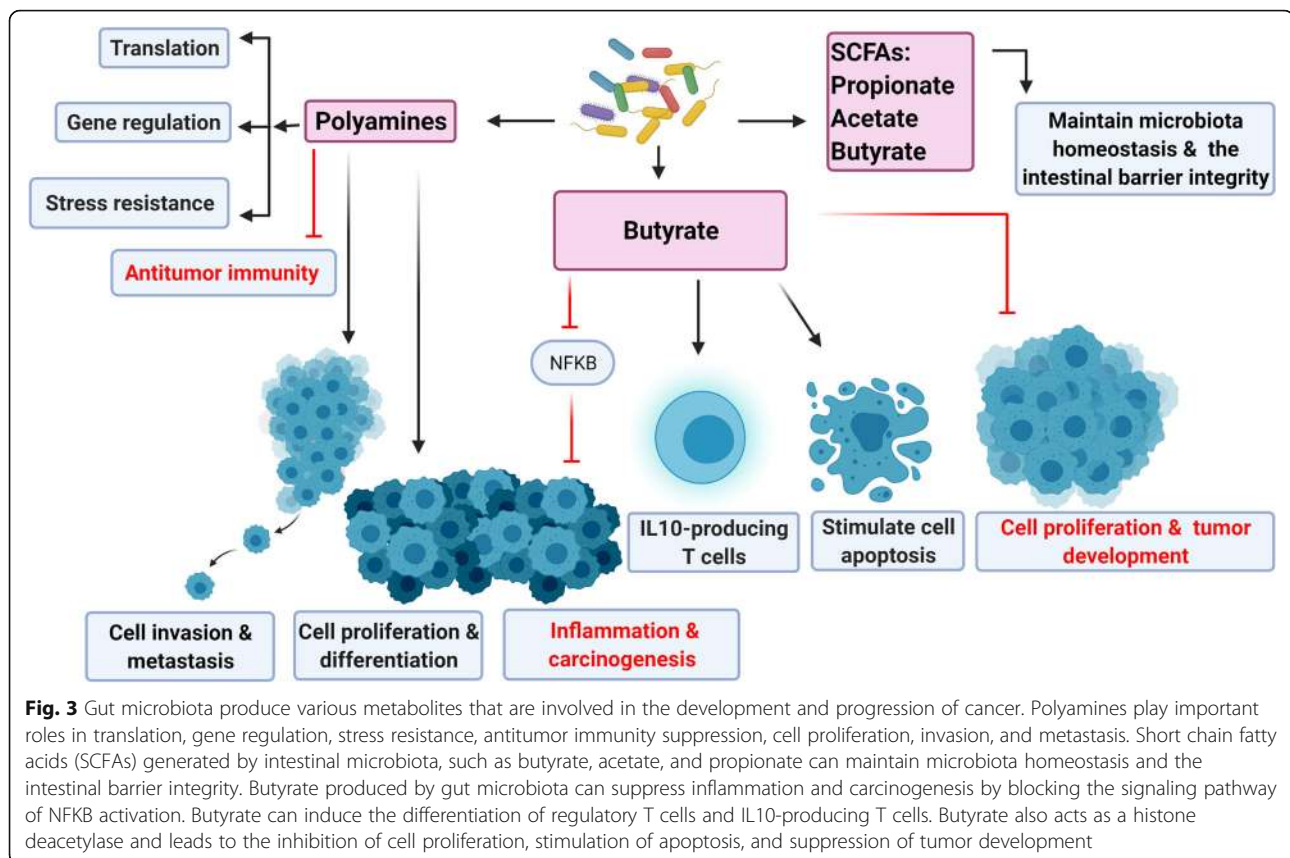
gut microbiome similarly affects *H. pylori*-induced gastritis (Fig. 2) [24]. UFA biosynthesis plays a decisive role in the integrity of membrane structure and function. *H. pylori* can grow at anaerobic conditions [152], allowing for *H. pylori* persistence and induction of carcinogenic consequences within the gastric niche.

Effect of gut microbiota on cell metabolites and carcinogenesis

Intestinal bacteria generate different metabolites affecting the progression and development of gastrointestinal tract tumors [154]. Polyamines, generated by gut bacteria and host cells, largely influence different pathologic and biologic processes, such as translation, stress resistance, gene regulation, and cell differentiation and proliferation [155]. Polyamines suppress antitumor immunity and promote cancer cells' proliferation, invasion, and metastasis [156]. SCFAs are dietary fiber fermentation products generated by intestinal microbiota, such as propionate, acetate, and butyrate. They can maintain microbiota homeostasis and the intestinal barrier integrity and suppress inflammation and cancer [157]. SCFAs such as butyrate, generated by the gut microbiota, may inhibit carcinogenesis and inflammation through blocking the activation of the NFκB signaling pathway, and

differentiating IL10-producing T cells and regulatory T cells [51, 158, 159]. Moreover, butyrate can act as a histone deacetylase inhibitor to suppress the proliferation of the cells, induce apoptosis, and suppress the development of the tumor [160–162]. In contradiction, low butyrate concentrations may potentiate the tumor growth that, in a mouse model, suppresses DNA mismatch repair deficiencies (Fig. 3) [163].

Functional analysis of the gastric microbiome indicated a significant reduction in the production of urease and bacterial flagella synthesis at early GC stages, whereas fructose glycolysis and glycosides hydrolysis showed an enhancement. The frequency of glucose-6-phosphate dehydrogenase exhibited a decrease, reflecting a decrement in carbohydrate degradation. The relative frequency of 6-phosphofructokinase (COG205) showed a drastic reduction in advanced GC cases [141]. Numerous bacteria (e.g. *Nitrospirae*, *Lactobacillus*, *Neisseria*, *Staphylococcus*, *Haemophilus*, *Clostridium*, and *Veillonella*) promote gastric carcinogenesis through stimulation of the N-nitroso compounds (NOCs) production [8, 164]. Higher levels of lactic acid bacteria were found in GC patients [165]. These bacteria may enhance the GC risk by several mechanisms such as elevated generation of ROS, NOCs, and lactate in addition to inducing EMT



and immune tolerance [102]. *In vitro* and *in vivo* investigations suggested the stimulating role of lactic acid bacteria in ROS generation which may lead to DNA damage. Enhanced the formation of NOCs can promote mutagenesis, angiogenesis, and the expression of proto-oncogenes, resulting in apoptosis inhibition [139, 166]. Lactic acid bacteria-produced lactate is a robust energy source for cancer cells [167] with a regulatory role in various carcinogenesis issues such as tumor angiogenesis and metastasis [168]. These bacteria are capable of promoting EMT with contributive roles in tumor invasion and metastasis [169] through induction of multipotency state [139].

Microbiome-based GC therapy

Conventional GC therapies such as surgery, chemotherapy, and radiotherapy have not shown high efficacy [102]. *H. pylori* eradication could be an effective approach to reduce the GC risk. Antibiotic treatment of *H. pylori* has been shown to alter the gastric microbiome composition [133, 164]. Regarding the increasing rate of antibiotic resistance of *H. pylori*, novel *H. pylori* eradication strategies are urgently required. Some probiotics have shown promises in the prevention of antibiotic-induced adverse impacts, an increase in *H. pylori*

eradication rate, and the reduction of fluctuations in the gut microbiome profiles [170]. *Lactobacillus* supplementation can effectively eradicate *H. pylori* [171, 172] and reduce the chance of GC development [102]. Some *Lactobacillus* strains mitigated *H. pylori* by inhibiting its adhesion to epithelial cells, production of organic acids or bacteriocins, and suppression of mucosal inflammation [173, 174]. *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* can decrement the *H. pylori* adhesion to gastric mucosal cells [175], *L. bulgaricus* showed inhibitory impacts on IL-8 production of mucosal cells by modulation of the TLR4/IkBa/NF-kB pathways [175]. A probiotic mixture containing *Lactobacillus* and *Bifidobacterium* showed helpful influences against *H. pylori*, at low side effects [176]. A combination of *Bacillus cereus*, *Enterococcus faecalis*, *L. acidophilus*, and *Bifidobacterium infantis* increased the host immunity and declined inflammation among GC cases undergoing gastrectomy [177].

Despite the traditional carcinogenic role of bacteria, new studies have revealed their anticancer features. The anticancer properties of bacteria can be assigned to various mechanisms such as colonization in tumors, releasing active agents, a carrier for anticancer drugs delivery, suppression of vital nutrients for tumor metabolism and

proliferation, reinforcement of host immunity, and bio-film formation [102, 178, 179]. The KLA peptide is a pro-apoptosis peptide KLAKLAKKLAKLAK with anti-cancer activities through apoptosis induction by disrupting mitochondrial membrane; it however showed poor membrane permeability [180]. HPRP-A1 (*H. pylori* ribosomal protein) and its enantiomer HPRP-A2 (15-mer cationic peptides) can be derived from the N-terminus of *H. pylori* ribosomal protein L1 [181]. HPRP-A1 and HPRP-A2 have exhibited powerful anti-microbial and anticancer features. HPRP-A1—a membrane-active peptide—is capable of disrupting the tumor cell membrane. It is largely employed in drug delivery to cancer cells [182]. HPRP-A1 can facilitate the entry of KLA peptides to cancer cells, hence, promoting tumor cell death [183]. Apoptosis induction of HPRP-A2 in the GC cells is achieved via elevation of ROS production; activation of caspases (3, 8, and 9); reduction of mitochondrial membrane potential, and cell cycle arrest within the G1 phase [184].

Conclusions

Mechanistic studies evaluating how gut microbes regulate health and promote gastrointestinal cancers are still at the early stage. Nevertheless, researchers have determined that gut microbiota are in close relation with humans and markedly influence GC and human health. Researchers have taken some steps to regulate gut microbes. The objectives are multifaceted, including the regulation of human metabolism, immune, and inflammatory reaction, as well as inhibiting carcinogenesis and cancer progression. Significant advances have been made in understanding the interaction between *H. pylori* and intestinal microbiota in the development of gastritis and cancer. However, there have been controversies in the findings of different studies which seem to be due to environmental differences (e.g., diet, etc.) or genetic differences of the host. Detailed studies in well-defined human populations are still required to compare the composition differences of the gut microbiome in different anatomical regions of the stomach of individuals developing *H. pylori* infection with and without neoplastic lesions. Future investigations are recommended to assess the effect of the gut microbiome composition in various anatomical stomach regions on the risk of cancer. These could be carried out by the site-specific topographical mapping of the microbiota in the absence or presence of *H. pylori* and by assessing variations with respect to the states of the disease along the gastric carcinogenesis cascade [185]. Deeper and better understanding of the relationship between *H. pylori*-related precancerous gastric lesions and gut microbiota, and the complicated interaction between them can have a significant impact on

the design of new strategies for the prevention, diagnosis and treatment of GC.

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Authors' contributions

S.L-N. provided direction in the preparation of the manuscript. S.Z.B. performed primary literature search. S.Z.B. wrote the first draft of manuscript. S.L-N. discussed and revised the manuscript. S.Z.B. managed the references. S.L-N. approved the version to be published. All authors have read and approved the manuscript.

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Availability of data and materials

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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

No potential conflicts of interest.

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