Microbiome Metagenomics and Epigenomics on Gastric Cancer

Subjects: Anatomy & Morphology

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The gut microbiome plays a pivotal role in the development and progression of gastric cancer. Similar microbes implicated in gastric cancer carcinogenesis have been detected in some of the risk factors of the disease, with microbial dysbiosis as a common root of concern as it promotes carcinogenesis through dysregulation of cancer immunosurveillance and induction of therapeutic resistance. The microbiome plays an important role in gastric cancer (GC) pathological phenotypes and should be taken into consideration when designing personalized cancer therapies.

Keywords: gastric cancer (GC) ; metabolites ; microbiome ; H. pylori ; dysbiosis ; epigenomics ; personalized therapy ; inflammation

1. The Link between Gut Microbiome and Gastric Cancer Risk Factors

One of the proposed cancer prevention strategies is risk factor (RF) reduction. Treatment of the underlying risk factor (RF) can therefore reduce the risk of developing cancer or aid in the treatment of cancer resulting from RF predisposition. A systemic review by Yusefi et al. reported a total of 52 gastric cancer (GC) RFs which were identified and classified according to 9 categories influenced by familial genetics, lifestyle, environment, medication, and exposure to toxins [1]. These categories can be further grouped into two sub-categories; genetic and modifiable, with genetic factors being hereditary while modifiable ones are acquired through lifestyle and can be changed. The most common RFs for GC include *Helicobacter pylori (H. pylori)* infection, metabolic syndrome, an increased salt intake with a diet low in fiber, as well as male gender (two-fold increase in males than females) [2][3][4][5][6]. Although GC is more common in males, some subtypes such as the MSI and CIMP-H tumors are more prevalent in females [7][8][9]. It was initially thought that GC affects people of an older age (50 to 70 years), however recent findings show an increased incidence in younger individuals [10][11]. The modifiable RFs often lead to epigenetic alterations, and examples of these include toxins, diet, obesity, infection and so on [12]. **Figure 1** shows how various RFs can lead to GC.

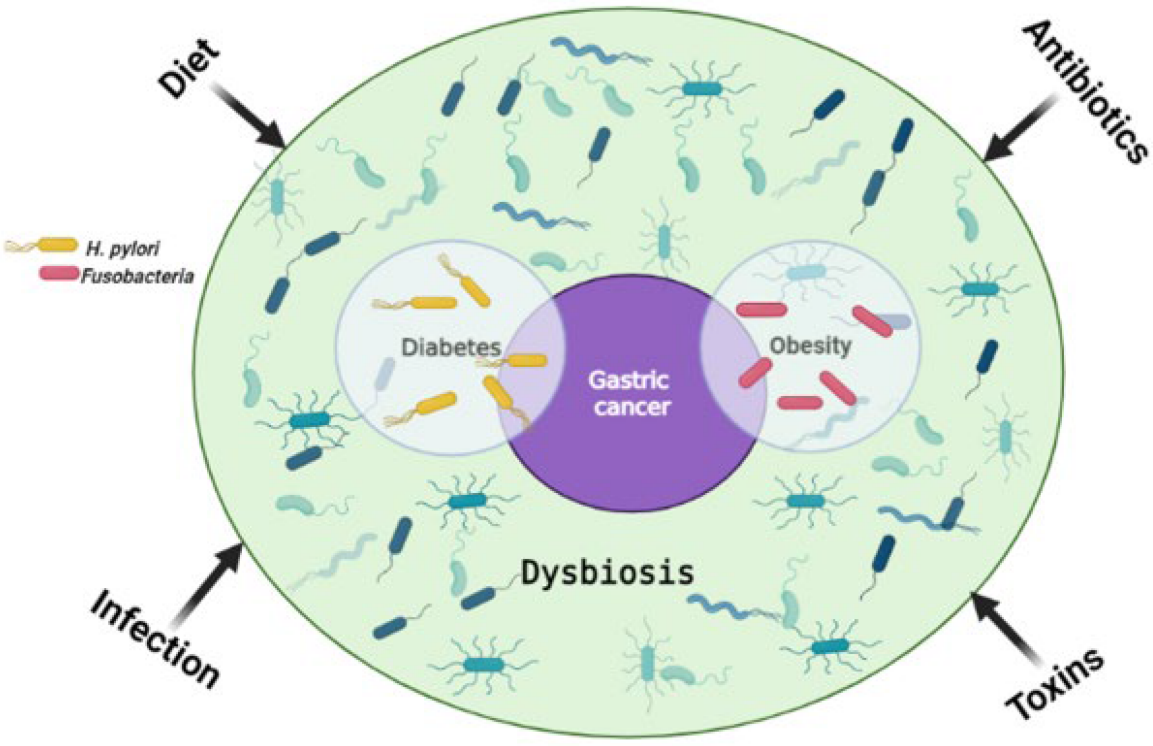

Figure 1. The main risk factors for gastric cancer. Environmental factors influence the gut microbiome and can lead to dysbiosis, one of the main causes of tumorigenesis. *H. pylori* infection is a shared risk factor between gastric cancer and diabetes, with diabetes being a risk factor for gastric cancer on its own. Similarly, *Fusobacteria* are a common risk factor for obesity and gastric cancer, with obesity on its own being a risk factor for gastric cancer. Created with BioRender.com. (accessed on 20 September 2022).

1.1. Obesity

The International Agency for Research on Cancer (IARC) regards obesity as the second leading cause of cancer after smoking [13]. About 3–9% of all cancers are approximated to stem from obesity, and GI cancer with obesity origin has the worst prognosis [14][15]. One of the risk factors for obesity includes a high fat and sodium diet, which alters the gut microbiota composition, resulting in gut microbial dysbiosis [16]. Dysbiosis regulates the susceptibility and initiation of many gut malignancies [17]. Kim et al. found that *Fusobacterium* was enriched in fecal samples of metabolically unhealthy overweight and obese individuals [18]. This shows that the bacteria are a common RF in obesity and GC.

1.2. Diabetes

Diabetes is considered an important contributing factor in GC development, and it is postulated that this is due to shared RFs. These include obesity, a higher infection/reinfection rate, and a lower eradication rate of *H. pylori*, as well as the chronic use of medication [19]. Additionally, increased salt intake may cooperate with *H. pylori* infection in the induction of GC and progression. However, a 2022 metanalysis showed no association between diabetes and GC risk in the grading of *H. pylori* infection and other shared RFs [20]. The authors concluded that diabetes may be associated with excess cardia GC risk.

1.3. Acid Reflux-Related Disorders

Several studies have indicated the association between gastroesophageal reflux disease (GERD) and GC [21][22][23][24]. The overall 5-year survival rate of gastric cardia adenocarcinoma is reported at approximately 31% [25]. Two subtypes of gastric cardia cancer exist; one with GERD origin and the other associated with atrophic gastritis [26]. Misumi et al. defined gastric cardia carcinoma as “a lesion with its center located within 1 cm proximal and 2 cm distal to the esophagogastric mucosal junction” [27]. In a study by Ye et al, it was reported that the risk of developing gastric cardia adenocarcinoma persisted following anti-reflux surgery [24]. This shows that GERD can lead to long-term effects on the stomach mucosa. Some of the risk factors of GERD are obesity and a diet low in fibre, which can have an effect on the gut microbiome [28]. Generally, acid reflux is linked to gut microbiome dysbiosis [29]. A retrospective study by Polat and Polat reported that 82.5% of 1437 GERD patients had *H. pylori* infection with 1–3 severity score [30], bearing in mind that *H. pylori* infection is a common RF for GC and GERD.

1.4. Chronic Infection and Inflammation

Infection with pathogenic microbiota leads to the upregulation of inflammatory markers such as cytokines and other secretory proteins. Cytokines such as tumor necrosis factor (TNF), interleukin- 1 (IL-1) and IL-6 expressed within the TME induce cell invasion, metastasis, angiogenesis, growth, and anti-apoptotic effects [31][32][33]. Colonization of *H. pylori* in the stomach leads to chronic inflammation via the activation of Wnt/β-catenin and other pathways that get activated by the bacteria’s virulence, which further permits the bacteria to survive and thrive in the gut [34][35]. The Wnt/β-catenin signaling pathway is crucial in modulating key cellular processes contributing to carcinogenesis, such as apoptosis, metastasis, proliferation, and genetic stability [36]. Moreover, Wnt/β-catenin has been implicated in pancreatic cancer chemoresistance [37].

The *H. pylori* commonly infects the stomach, leading to chronic diseases such as peptic ulcer, gastritis, and gastrointestinal (GI) cancers such as GC. The stomach’s naturally acidic environment assists in preventing infection by pathogens. The *H. pylori* bacteria can maneuver this acidic environment and alter the overall profile of the gastric microbiome [38][39]. There are three mechanisms that the bacteria utilize to alter the GI microbial profile to favor their survival [40]. This includes the employment of enzymes such as ureases which help the bacteria to buffer the acidic pH of the stomach [41]. Secondly, the *H. pylori* infection effects changes on the cell cycle of gastric epithelial cells, resulting in the elevated expression of p21 and p53 proteins and leading to gene mutations [42][43]. In addition, the infection can lead to abnormal molecular signaling pathways [44]. According to Rossi et al., genomics and proteomics cannot be used to monitor response to therapy [45]. However, a study by Goodman et al. provided evidence that cell-free DNA (cfDNA) can be used to monitor response to chimeric antigen receptor T-cell (CAR-T) therapy in patients with a certain type of B-cell lymphoma [46]. Similarly, the Lewis protein CA-19 is routinely used as a gold standard marker for monitoring response to

pancreatic cancer therapies [47][48]. The potential of these “omics” in the area of therapeutics is limited and not well understood.

Gram-negative bacteria including *H. pylori* are highly resistant to numerous drugs and antibiotics due to the protection provided by their outer membrane [49]. The chronic inflammatory response induced by *H. pylori* predisposes the mucosal cells to carcinogenesis. In a prospective, double-blind, placebo-controlled, randomized trial published in 2018 by Choi et al., it was observed that GC patients who had either endoscopic resection of early GC or high-grade adenoma, after receiving *H. pylori* ablation therapy, had lower metachronous GC rates compared to their counterparts who received a placebo [50]. Later on, the same team conducted a randomized trial that was published in 2020 where they evaluated the treatment of *H. pylori* in first-degree relatives of GC patients [51]. Their results showed that the treatment lowered the risk of developing GC by 55% when compared to the placebo group. Moreover, the risk of developing GC was lowered in 73% of participants who were confirmed for *H. pylori* ablation than those who had persistent infection of the bacteria. These results confirm the potential use of RFs as therapeutic targets for cancer therapy.

The *H. pylori* bacteria initiates GC by causing the DNA to replicate faster due to the chronic inflammation incited by the organism, and this leads to mutagenesis and genomic instability. Inflammation is a hallmark of cancer which plays a key role in all three carcinogenesis stages [52]. The virulence factors of *H. pylori,* such as the cytotoxin-associated gene A (cagA), are responsible for its chronic inflammation properties. CagA functions as an oncoprotein and can trigger MAPK signaling of host cells, leading to persistent inflammation and uncontrollable proliferation [44]. Additionally, the MAPK pathway is responsible for chemoresistance in pancreatic cancer and GC cells [53][54]. It is postulated that cagA travels through the type IV secretion systems (T4SS) upon contact with the host cell and this triggers the endocytosis of the protein (**Figure 2**) [55]. The protein can activate the MAPK/ERK pathway in two ways: by direct binding in a phosphorylation-independent state or through recruiting the phosphatase SHP2 [56][57]. The SHP2 protein plays a crucial role in the pathologic activity of cagA and can independently modify ERK signals autonomous of Ras [58].

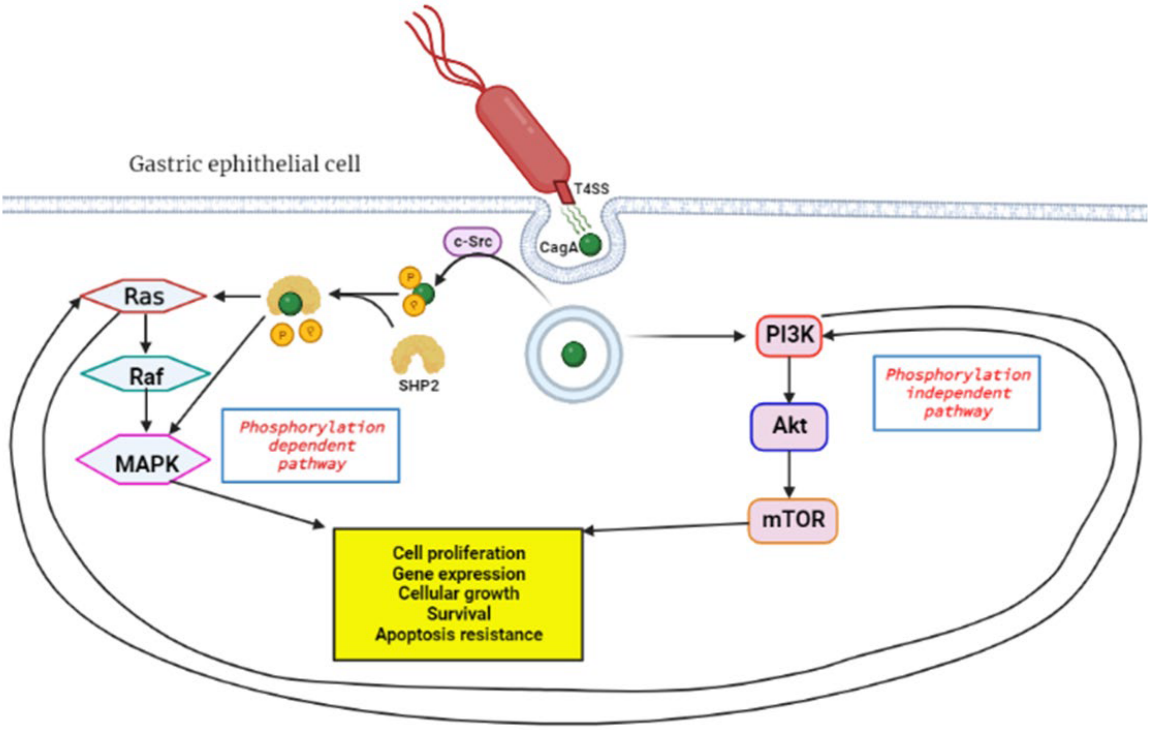

Figure 2. Activation of RAS/RAF/MEK/ERK pathway by *H. pylori* cagA oncoprotein. Upon contact with the gastric epithelial cell membrane, the bacteria’s T4SS system releases cagA through a channel, and this triggers endocytosis, a process where proteins get engulfed into the cell. In the phosphorylation dependent pathway c-Src, tyrosine kinase phosphorylates cagA, followed by SHP2 phosphatase cleavage of the phosphate groups from cagA. This leads to downstream activation of the RAS/RAF/MEK/ERK signal transduction pathway which favors tumorigenesis. The phosphorylation independent pathway is the PI3K/Akt/mTOR, which gets activated by cagA and results in products that induce tumorigenesis. Created with BioRender.com. (accessed on 27 September 2022).

The MAPK/ERK is also known as the RAS/RAF/MEK/ERK signaling pathway and plays a major role in regulating cell differentiation, proliferation and survival. This pathway is interlinked with the PI3K/Akt/mTOR pathway and can cause compensatory signal transduction in cases where the other is compromised [59]. The coupled inhibition of the two pathways has been effective in tumor stasis and overcoming drug resistance of GI tumor cells [60][61]. An elevated

expression of the Ras protein is positively associated with increased Akt protein levels. Thus, PI3K/Akt/mTOR is an alternative pathway to Ras/Raf/MEK/ERK for EGFR signaling [62]. This may affect the efficacy of anticancer treatment, and therefore this must be considered when developing novel anticancer therapies. The bacteria can also initiate GC through aberrant DNA methylation, which will be discussed in more detail later in the review. Moreover, the expression of DNA mismatch repair (MMR) genes MutS and MutL are decreased in *H- pylori*-positive gastric mucosa [63].

The antibiotic metronidazole functions by interacting with the DNA of the target organisms (Gram-negative bacteria) breaking down DNA strands and causing the loss of DNA integrity and the ultimate inhibition of protein synthesis [64]. Metronidazole gets activated upon reduction by the protein ferredoxin (**Figure 3**). The concentration gradient created upon reduction increases the diffusion of metronidazole into the bacterial cell and cytotoxic free radical generation [64]. The drug has been shown to be successful in treating *H. pylori*; however, the bacteria has evolved to be resistant to it and can only be effective when in combination with esomeprazole and amoxicillin [65][66].

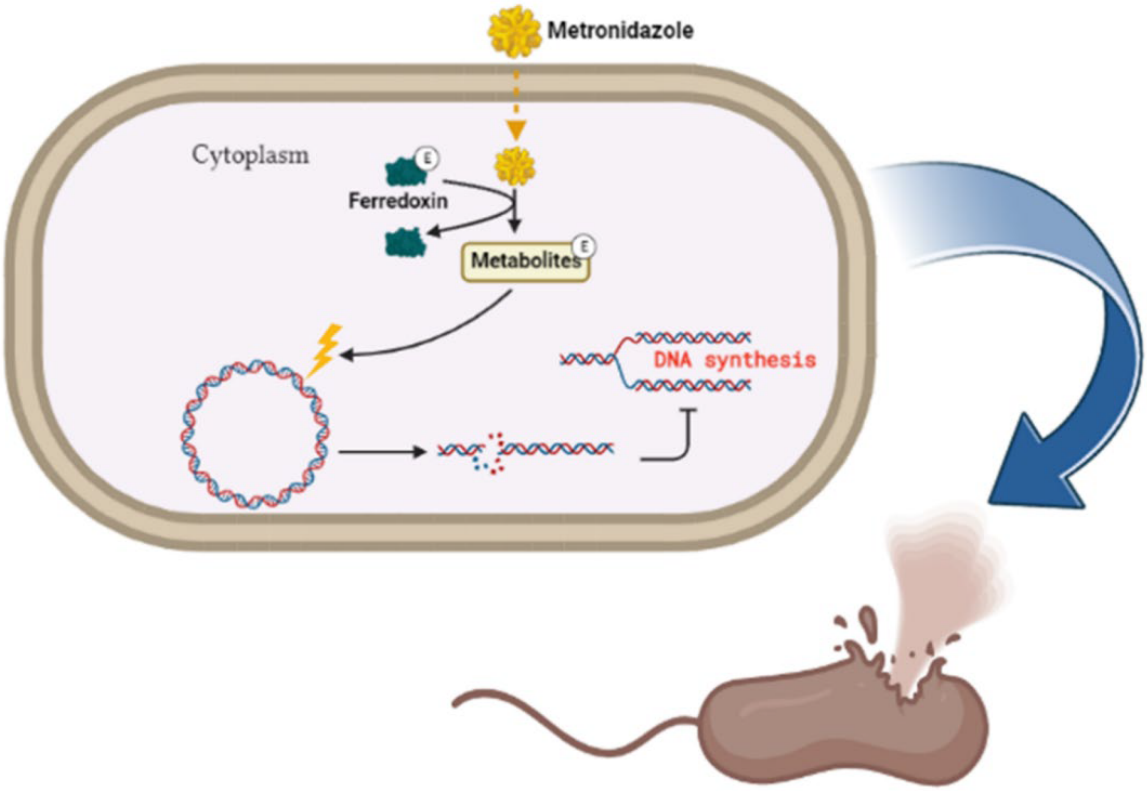

Figure 3. Metronidazole's mode of action. The inert drug enters susceptible bacterial cells through passive diffusion. Metronidazole is activated through its reduction by ferredoxin. Upon activation of the drug, a concentration gradient is formed, and this favors the increased uptake of the drug into the organism, thus elevating its antimicrobial effect. DNA damage subsequently leads to protein synthesis inhibition and consequent apoptosis. Created with BioRender.com. (accessed on 27 September 2022).

Another type of Gram-negative bacteria, Fusobacteria, is considered a RF for GC. The *Fusobacterium* spp., predominantly *F. nucleatum,* are frequently found in abundance in GC, pancreatic and colorectal tumors compared to non-cancerous tissues [17][67][68]. *F. nucleatum*-positivity has been linked to overall worse survival in Lauren's diffuse type of GC and MSI-high status of colon cancer [67][69]. It is therefore safe to assume that *F. nucleatum* predisposes individuals to the MSI-high subtype of GC. Just like *H. pylori*, Fusobacteria can be eradicated with metronidazole therapy. The bacteria is known to be highly sensitive to the drug [70]. Apart from bacteria, other viruses such as Epstein-Barr virus (EBV), which is sometimes referred to as human herpesvirus 4 (HHV4), raises the risk of GC by a factor of 18 times and the EBV-associated GC (EBVaGC) is observed more in males than in females [71]. EBVaGC contributes to approximately 10% of all GC cases worldwide and is more common in the early stages of the disease [72]. Other viruses with potential association with GC include the human papillomavirus (HPV), hepatitis B virus (HBV), John Cummingham virus (human polyomavirus 2) and human cytomegalovirus [73]. More research on these viruses is required to determine their role in GC pathogenesis.

2. Other Microbes Implicated in GC Pathogenesis

Carcinogenesis describes the process of cancer formation which stems from irreversible genetic alterations or interruptions due to internal and external factors. It is a multistage molecular process involving (i) initiation, (ii) promotion and (iii) progression [74][75]. The microbes can either directly affect the cells and lead to carcinogenesis or tamper with the body's cellular pathways to support its growth and sustainability. The gut microbiome, which is also known as the human second genome, plays a major role in the pathogenesis of GI cancers including colorectal, pancreatic, liver and gastric [17][76][77][78]. Bacterial and viral pathogens negatively influence the host's genomic stability and integrity by the destruction of DNA strands, thereby initiating tumor development [79]. Approximately 95% of the human body's microbiota resides in the gut and the microbes generally assist in maintaining the balance between health and disease [80]. There appears to be microbiome dysbiosis in most cancers, and this has been found to aggravate tumorigenesis. Although the microbiome is implicated in a number of cancers, the exact mechanisms by which they lead to cancer is still controversial. This is due to the low biomass of the microbiota in the TME, making it challenging to study them further [81]. Thanks to omics studies, this challenge can be overcome, as they shed light on the role of the gut microbiome in cancer pathology, prevention, and therapy [82].

2.1. The Boas-Oppler Bacillus

The lactic acid bacillus (lactobacillus), which is commonly called the Boas-Oppler Bacillus, dates back to 1895 when Izmar Isidor Boas and Bruno Oppler described the role of these Gram-positive bacteria in GC [83]. In their study, the researchers discovered that the bacillus was present in abundance in the gastric juices of 95% of GC individuals included in the study. This has been observed to be common, especially in patients with an advanced stage of the disease [84]. Lertpiriyapong et al. reported that infection of insulin–gastrin (INS-GAS) transgenic mice with *L. murinus* ASF361 led to the development of gastric neoplasia via the upregulation of oncogenes and pro-inflammatory genes [85]. Lactobacilli produce lactic acid/lactate which plays a huge role in the Warburg effect, a hallmark of cancer. Additionally, the Lactobacilli play a role in the production of excessive amounts of N-nitroso compounds (NOCs), which are carcinogenic and predispose *H. pylori*-free individuals to GC [86][87]

2.2. Mycoplasma

The study of the role of mycoplasma infection in cancer development dates way back to the 1950s [88]. They are Gram-negative bacteria that belong to the class Mollicutes [89]. The bacteria are commonly known for causing infections of the ear, respiratory system, lungs, urogenital tract and also to cause sexually transmitted infections (STIs) [90]. The well-studied pathogenic species include *Ureaplasma urealyticum, M. fermentans, M. penetrans, M. hominis, M. genitalium, M. pneumoniae*, *M. hyorhinis and os on.* The *M. hyorhinis* species is implicated in the development of GC [88][91][92][93][94]. Although mycoplasma have been detected in GC biopsies, the infection is not considered a RF for the disease [95]. Research has shown that mycoplasma cause inflammation, which instigates cancer initiation and progression [96][97].

A p37 lipoprotein located on the outer membrane of *M. hyorhinis* has been proven to play a key role in tumorigenesis [93][98][99]. The p37 protein heightens the expression of inflammation-associated genes such as vascular cell adhesion molecule 1 *(Vcam1)*, *IL-6*, *IL-1*, and lipocalin 2 *(LCN2)* [96]. Additionally, p37 promotes cell invasiveness by blocking contact inhibition, and this has been observed in melanoma, gastric and prostate carcinomas [93][98][99]. Gong et al. demonstrated that p37 promotes the metastasis of human GC and lung cancer cells through the activation of matrix metalloproteinase-2 (MMP-2) and EGFR/PI3K/AKT/ERK pathways [91]. Another mechanism by which the mycoplasma promotes metastasis is via the accumulation of β-catenin and the activation of its Wnt signaling pathway [98][100]. Moreover, metastasis in GC by *M. hyorhinis* can be initiated through activation of the NACHT, LRR, and PYD domains-containing protein 3 (NLRP3) [101]. The NLRP3 is an inflammasome critical in caspase-1 modulated inflammation in response to pathogenic organisms [102]. Because these organisms lack peptidoglycan and are Gram-negative, this makes them extremely resistant to antibiotics [90]. The *M. hyorhinis* infection has been linked with the diffuse-type GC with a higher infection rate in advanced stages (TNM III/IV) than in earlier stages of the disease [94]. On the other hand, *M. hyorhinis* can cause chronic infections which induce chromosomal instability, and one can classify this under the TCGA CIN subtype of GC [7][101]. The age group of GC patients who are more likely to be infected with mycoplasma is the elderly [94].

3. Compounds Linked with GC Induction

3.1. Contribution of Microbes in Asbestos-Induced GC

Amosite, actinolite, chrysotile, anthophyllite, crocidolite, and tremolite are the six types of asbestos of which chrysotile (white asbestos) is the most abundant (99%) and is also exceedingly hazardous and lethal [103][104]. However, this does not mean that the other types are less harmful, as they also possess toxicity to some extent [105]. The link between asbestos and GI cancers was first demonstrated by Selikoff et al. in 1960, then in 2012, a review by Kim et al. reported that among all GI cancers, GC is the one that is greatly linked with asbestos exposure [106][107]. Oksa et al. summarized the association between GC and asbestos exposure and concluded that the risk of developing GC is directly proportional to asbestos exposure with the risk ranging from 15% to 20% [108]. In a study by Patel-Mandlik and Millette, an olive baboon that was fed chrysotile was discovered to have asbestos fibers deposited in its stomach while other pieces were able to relocate to most neighboring tissues except for the small intestine [109]. This shows that the fibers cannot be digested and can remain in the stomach for longer periods of time before their excretion [110]. Because of its strength and chemical properties, the material does not get digested or broken down, and the exposure elicits scarring and irritation, resulting in inflammation of the tissue [110]. Data shows that prolonged asbestos exposure leads to chronic inflammation and cellular stress, which activates the MAPK pathway and related transcription factors leading to immune response gene expression [111]. The gut microbiome plays a vital role in modulating immune homeostasis and GC inflammation. However, its association with asbestos in cancer is poorly reported.

Stanik et al. evaluated the ability of *L. casei* and *L. plantarum* to biologically break down white asbestos fibers [112]. The bacteria were successful due to their ability to produce lactic acid, which contains hydrogen ions that can remove magnesium ions from the crystalline structure of the asbestos fibers. A study by Seshan showed that when chrysotile is exposed to strong acids like those of the stomach or water, the physical and chemical properties of the asbestos change as the magnesium is lost from the asbestos [113]. There is evidence that shows that *L. plantarum* is capable of preventing *H. pylori*-induced inflammation of the gastric mucosa and restores balance to the gut microbiome, which is altered during such an infection [114]. Pretreatment with these bacteria was able to slow down the expression of inflammatory cytokines and cell infiltration. Similarly, *L. casei* has an anti-cancer effect, as it is able to inhibit the mTOR and NF-kB signaling pathways, thereby leading to the cellular apoptosis of GC cells [115]. **Figure 4** shows how *L. casei* and *L. plantarum* could potentially prevent GC carcinogenesis. From this information, it could be deduced that these two Lactobacilli species can be used to aid in the treatment of GC, more in particular one with an asbestos origin.

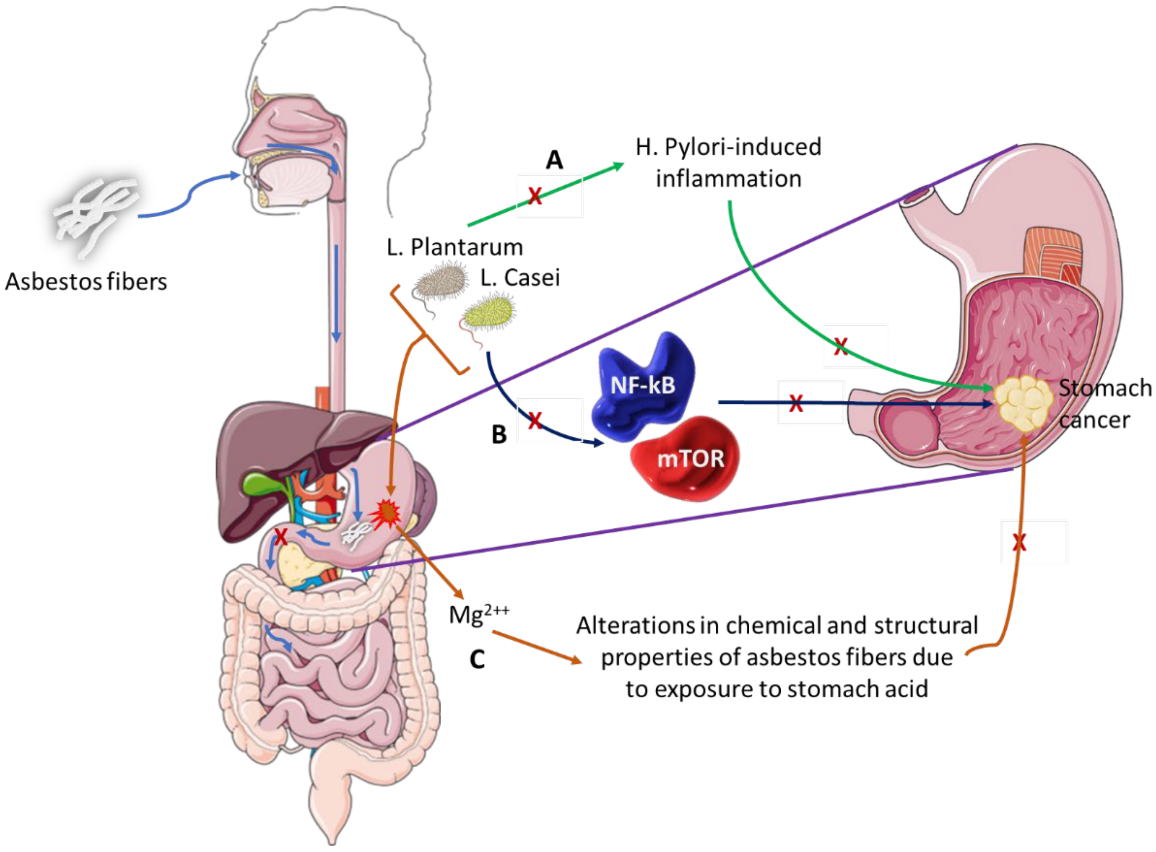

Figure 4. The role of microbiota in asbestos-induced GC.

Asbestos fibers can be ingested and pass through the esophagus and lodge into the stomach lining. These fibers do not pass through to the small intestines where they could possibly go through the process of excretion but remain in the stomach long enough to induce GC.

(A)*L. Plantarum* has the ability to block *H. Pylori*-induced inflammation that is associated with GC development.

(B)*L. Casei* bacterium downregulates pro-oncogenic signaling pathways (NF-kB and mTOR) thus inhibiting cancer development and progression.

(C)This pair of bacteria can alter the chemical and structural properties of white asbestos by the removal of magnesium ions, a process that could be explored as preventative therapy in individuals exposed to asbestos fibers or as therapeutic intervention in asbestos-induced GC.

3.2. Enterobacteriaceae and Nitrosamines Production

Nitrosamines are carcinogenic N-nitroso compounds which can nest in the stomach and are produced when amines react with nitrites. They can either be ingested as an outside source or produced from ingested food with the help of certain bacteria [116]. Foods that contain nitrites include processed meats, fish, fried bacon, beverages, and cheese [116]. Cigarettes and E-cigars also release some nitrosamines called tobacco-specific nitrosamines (TSNAs) when inhaled and can result in DNA damage and mutagenesis [117]. Exposure has been correlated with GC RFs such as diabetes and pathogenesis to the mammary glands, leading to breast cancer [118][119][120]. In breast cancer TSNAs actively bind nicotinic acetylcholine receptors (nAChRs), activating its signaling pathways. The alpha7 receptor (α7nAChR) is an oncoprotein that plays a role in both the initiation and progression stages of breast cancer carcinogenesis [121]. The estrogen receptor-positive type of breast cancer carcinoma has been shown to express the α7nAChR in high levels [121]. Nitrosamines have been reported in lung cancer as activators of the NF-kB and PI3K/AKT signaling pathways, which are pivotal in cell proliferation [122].

There is a positive correlation between ingestion from nitrosamine sources and GC [123][124][125]. The nitrosamine hypothesis dates back to the 1950s and paved the way for research investigating the role of the gut microbiome and GC until the focus shifted towards *H. pylori's* role in chronic inflammation. Nitrate reductases are secreted by Gram-negative bacteria called *Enterobacteriaceae.* These enzymes catalyze the conversion of nitrate to nitrite [126]. These bacteria play a key role in nitrosamine production in the gut. In a study by Sarhadi et al., *Enterobacteriaceae* was found to be abundant in fecal samples of different GC types [127]. Similar findings were reported by Liu et al., who detected *Escherichia* and *Streptococcaceae* in abundance in GC patients [128]. Qin et al. reported an abundance of *Enterobacteriaceae* in diabetic patients, one of the risk factors of GC [129].

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