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Overgrowth of *Lactobacillus* in gastric cancer

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Abstract

Dysbiosis of the gastric microbiome is involved in the development of gastric cancer (GC). A number of studies have demonstrated an increase in the relative abundance of *Lactobacillus* in GC. In this review, we present data that support the overgrowth of *Lactobacillus* in GC from studies on molecular and bacterial culture of the gastric microbiome, discuss the heterogenic effects of *Lactobacillus* on the health of human stomach, and explore the potential roles of the overgrowth of *Lactobacillus* in gastric carcinogenesis. Further studies are required to examine the association between *Lactobacillus* and GC at strain and species levels, which would facilitate to elucidate its role in the carcinogenic process.

Key Words: *Lactobacillus*; Gastric cancer; Gastritis; Microbiome; Next generation sequencing

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Core Tip: Many strains of *Lactobacillus* have been used as probiotics in the clinical setting. However, recent molecular analyses of the gastric microbiome demonstrate a close association between an increased abundance of *Lactobacillus* and gastric cancer. In this paper, we review the current understanding of heterogenic effects of *Lactobacillus* on the health of the human stomach and discuss potential roles of the overgrowth of *Lactobacillus* in the gastric carcinogenesis.

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INTRODUCTION

Gastric cancer (GC) is a major health burden worldwide, which is the fifth most common cancer worldwide[1]. Host genetic variations, environmental factors, and microbial infection participate in the development of GC[2-6]. *Helicobacter pylori* (*H. pylori*), which is highly prevalent in the human population, is classified as a class I carcinogen[7]. The pathogen has been suggested to act as a trigger of the carcinogenic cascade of the stomach.

The human stomach harbors a number of bacteria. These bacteria may participate in the development of GC through production of carcinogenic compounds[8]. Recent molecular analysis reveals bacteria of the gastric microbiome are mainly from the phyla Proteobacteria, Firmicutes, Bacteroidetes, Actinobacteria, and Fusobacteria[9]. In GC, the microbiome was altered substantially[10,11]. Data of studies on gnotobiotic mice demonstrate that the presence of artificial microbiota in the stomach promotes the development of *H. pylori* induced cancer[12]. Thus, dysbiosis of the gastric microbiome is likely involved in the development of GC[13].

A prominent change of the gastric microbiome is the altered relative abundance of certain bacteria in GC[14]. Results from a number of studies show an increase in the abundance of *Lactobacillus* in GC. Considering the wide use of *Lactobacillus* in the clinical setting as a probiotic organism, it is surprising that the bacterium is enriched in GC. It is of great importance to clarify whether the enrichment of *Lactobacillus* is involved in the gastric carcinogenesis[15]. In this paper, we review the literature published recently to verify the finding that *Lactobacillus* is enriched in GC, discuss possible mechanisms for the overgrowth of *Lactobacillus*, and explore potential roles of *Lactobacillus* in the carcinogenesis of the stomach.

INCREASED ABUNDANCE OF *LACTOBACILLUS* IN GC

In GC, the gastric microbiome shows a substantial alteration[16]. Bacteria with varied abundance are potentially associated with cancer development. A close association has been suggested between *Lactobacillus* and GC[10]. To verify this notion, we review the literature involving studies designed to identify compositional changes of gastric mucosa associated microbiota in GC. The key words "gastric cancer" and "microbiota" or "microbiome" were used to search the PubMed database from January 2014 to January 2021. A total of 20 articles were included for further analyses, after exclusion of the articles published in non-English languages, letters, case reports, reviews, or conference reports. Studies were also excluded when the microbiome examined was not from the stomach (*i.e.*, oral or fecal microbiome).

According to experimental design, these studies were divided into three categories. Category I consists of three case-control studies comparing GC with healthy controls (normal stomach) (Table 1)[17-19], category II includes nine case-control studies comparing GC with non-cancerous stomach (Table 2)[10,16,20-26], and category III is composed of eight studies observing the compositional changes of the gastric microbiome in multiple stages of the carcinogenic process of the stomach, including normal stomach, intestinal metaplasia, intraepithelial neoplasia, and GC (Table 3)[11,14,27-32].

Studies from category I have demonstrated that *Lactobacillus* was rarely present in the gastric microbiome of healthy controls (Table 1)[17-19]. The abundance of *Lactobacillus* was dramatically increased in GC[18]. However, results of the other two studies do not support this finding. Analyses of category II studies reveal that 7/9 studies show an enrichment of *Lactobacillus* in GC in comparison with chronic gastritis, functional dyspepsia, or non-cancer conditions. The fold change in the abundance of *Lactobacillus* varies from 1.9 to 194.6.

Results from the majority of (5/8) category III studies demonstrated that the relative abundance of *Lactobacillus* is significantly increased in GC compared to that in precancerous lesions, chronic gastritis, or normal mucosa (Table 3). There was a trend that the

Table 1 Relative abundance of *Lactobacillus* from category I studies

Ref.	HC (n)	GC (n)	<i>Lactobacillus</i>	Fold change	LDA score
Gunathilake et al[17]	88	268	-		
Gunathilake et al[18]	288	268	+	47.6	3.2
Cavadas et al[19]	164	83	-		

HC: Healthy controls; GC: Gastric cancer; “+”: Significantly statistical difference between groups; “-”: No significant difference between groups.

Table 2 Changes in relative abundance of *Lactobacillus* from category II studies

Ref.	Control group (n)	GC group (n)	<i>Lactobacillus</i>	Fold change	LDA score
Jo et al[20]	29 (NC)	34	-		
Sohn et al[21]	5 (NC)	7	+	194.6/1.9	
Wang et al[16]	6 (CG)	6	+		
Ferreira et al[22]	81 (CG)	54	+	188.0	4.4
Hu et al[23]	5 (CG)	6	-		
Wu et al[24]	32 (SG)	18	+	2.5	> 2.4
Wang et al[10]	60 (CG)	60	-		> 3.6
Castaño-Rodríguez et al[25]	20 (FD)	12	+	17.7	3.6
Spiegelhauer et al[26]	22 (FD)	12	+	148.1	

NC: Non-cancer; CG: Chronic gastritis; SG: Superficial gastritis; FD: Functional dyspepsia.

Table 3 Variations in relative abundance of *Lactobacillus* from category III studies

Ref.	HC	SG	AG	IM	IN	GC	<i>Lactobacillus</i>	Fold change (GC vs SG/CG)	LDA score
Aviles-Jimenez et al[27]		5		5		5	+		
Eun et al[28]		10		10		11	-		
Li et al[29]	8	9		9		7	-		
Coker et al[30]		21	23	17		20	+		
Hsieh et al[11]		9		7		11	+	81.0/91.1	
Wang et al[14]	30	21		27	25	29	+	22.0	4.1
Dang et al[31]		17		13		30	-		
Gantuya et al[32]	20	20	40	40		48	+	17.9	4.4

HC: Healthy controls; SG: Superficial gastritis; AG: Atrophy gastritis; IM: Intestinal metaplasia; IN: Intraepithelial neoplasia; GC: Gastric cancer.

relative abundance of *Lactobacillus* was enhanced gradually from the normal mucosa to cancer of the stomach, suggesting a close association between the bacterium and the carcinogenic process[14,32]. Two studies from category III have employed the random forest model, a machine learning algorithm, to identify bacteria members of gastric microbiome capable of discriminating cancer from non-cancer diseases. The results demonstrated that a set of bacteria including *Lactobacillus* has high capacity to distinguish GC from precancerous diseases[14].

Compositional changes of the gastric microbiome are a distinctive feature in GC. However, bacteria with altered abundance in GC varied greatly among studies. Few bacterial members in the gastric microbiome, except for *Lactobacillus*, have been universally identified to have a varied abundance in GC. An increase in the relative abundance of *Lactobacillus* suggests the overgrowth of *Lactobacillus* in GC.

OVERGROWTH OF *LACTOBACILLUS* IN GASTRIC DISEASES

The human stomach is a hostile niche for the inhibition of bacteria. The gastric fluid has a median pH value of 1.4 which is able to kill most ingested bacteria[13]. Rapid peristalsis and epithelial regeneration further prohibit bacteria colonization of the gastric mucosa[33]. In healthy individuals, the stomach was once considered to be microbiologically sterile. Data from recent molecular analyses, however, demonstrated that gastric fluid and the luminal surface of the stomach harbor a low microbial population. The total bacterial count is lower than 1×10^4 per millimeter in gastric fluid, which is much lower than that in the intestine[13]. The species richness, which is the number of bacteria species in the stomach, is pretty low in contrast to the intestinal microflora[34].

A reduction in gastric acid may lead to bacterial overgrowth in the stomach. In pernicious anemia caused by autoimmune gastritis, loss of parietal cell results in decreased acid secretion from the stomach[35]. Distal gastrectomy also has lowered gastric acid output[35]. In these conditions, bacterial overgrowth occurs in the stomach [35]. As the intragastric pH rises, increased number of bacteria survive and proliferate to the point of being cultivated from the stomach[36]. In addition to the pH value, the total number of bacterial count in the stomach is also dependent on the time that bacteria are exposed to an environment at a pH lower than 4.0. Bacterial growth is inhibited when the pH is < 4.0 for a few hours a day[37-39]. Bacteria colonizing in the stomach are mainly from ingestion, the migration of commensal bacteria in the oropharyngeal cavity, or otherwise of the bowel through enterogastric reflux[35]. Bacteria moving into the stomach suffer from acid stress. Those finally colonizing the human stomach must possess properties of acid resistance or tolerance. There is, however, a substantial variation in the ability of different microorganisms to survive in the acidic environment. Colonization of the human stomach by *H. pylori* is dependent on its urease activity that produces an alkaline buffer zone of ammonia around cells. *Yersinia enterocolitica* also possesses a urease gene cluster, making it possible to grow in the stomach. Lactic acid bacteria are usually capable of proliferating in the weak acidic environment. Many lactic acid bacteria possess the urease activity. Some enteric pathogens have the ability to adapt themselves and consequently stay alive in different ways in this acidic condition. Recent studies demonstrate that prolonged treatment with proton pump inhibitors results in elevated pH of the gastric lumen, which would cause bacterial overgrowth[40]. Particularly, *Streptococcus*, one of the lactic acid bacteria, is associated with the use of proton pump inhibitors[41].

A prominent pathophysiological change in the stomach is a gradual drop in the gastric secretion during the carcinogenic process of the stomach. It has been found that patients with GC had reduced gastric acid secretion caused by oxyntic atrophic gastritis[42]. There is varying degrees of impaired acid secretion being reported in GC [43]. The pH value of gastric fluid may increase to 3.5-7.0. The acid hypo-secretion in intestinal-type GC has been further confirmed by the determination of serum biomarkers[44-47]. Reduction in the acid output is likely to be the major cause of the enrichment of *Lactobacillus* in GC. *Lactobacillus*, a lactic acid bacterium, is capable of tolerating acid and proliferating under weak acid conditions[48]. An elevation of the pH value in the stomach during proton pump inhibitor treatments increases the relative abundance of *Lactobacillus*[49]. With the increase in pH during the carcinogenic process, *Lactobacillus* may thus grow over other bacteria and become enriched in the cancerous stomach.

HETEROGENEOUS EFFECT OF *LACTOBACILLUS* ON HOST

The genus of *Lactobacillus* is a common member of gut microbiota. In many vertebrates (for example, mice, rats, and chickens) and insects, the genus is the most abundant bacteria in the gastric microbiota[50-53]. In humans, however, the frequency of *Lactobacillus* detected in the stomach is about 25.5%[54]. Prolonged symbiosis of the bacterium with animals promotes the mutualism and commensalism. In other words, *Lactobacillus* provides benefits for its host. Studies on the human stomach demonstrate that *Lactobacillus* possesses antimicrobial activities, alleviates mucosal inflammation, modulates mucosal immunity, and even has anti-cancer effects.

Benefits of *Lactobacillus* for its host

It has been found that the co-existence rate of *Lactobacillus* spp. and the gastric pathogen *H. pylori* is pretty low in the gastric mucosa of symptomatic patients with

gastrointestinal discomfort[54,55]. Two studies involving 197 and 427 patients with gastrointestinal discomfort, respectively, revealed that the co-existence rate of these two bacteria is only 8% [55] and 6.1% [54], respectively. In contrast, *H. pylori* has been detected in approximately half of patients in both studies. These data indicate the pathogen exclusion effect of *Lactobacillus*. Clinical trials with supplement of strains of *Lactobacillus* may increase the eradication rate of *H. pylori*. In addition, *Lactobacillus* could reduce the incidence of adverse events caused by anti-*H. pylori* therapies, alleviating disease-related clinical symptoms[56,57]. Thus, *Lactobacillus* benefits its host through anti-*H. pylori* effects. Further studies reveal that *Lactobacillus* can create competitive conditions, inhibiting pathogen adherence to mucus and epithelial layer of the stomach[58]. *L. plantarum* strains and *L. rhamnosus* strains increase the expression of *MUC2* and *MUC3* genes by epithelial cells, inhibiting the binding of pathogens[59]. Many *Lactobacillus* species produce bacteriocin which is capable of killing pathogens [60].

Lactobacillus alleviates mucosal inflammation of the stomach[61]. The microbe modulates signaling pathways, which results in a reduction in the expression of IL-8 [62]. Some probiotic strains of *Lactobacillus* and their metabolic products stimulate dendritic cells, leading to activation of anti-inflammatory pathways, and inhibition the inflammatory function of Th1 and Th17 lymphocytes[63]. The bacterium may change cytokine profiles, which increases the production of secretory IgA by B cells[62]. These findings suggest that *Lactobacillus* possesses an anti-inflammatory effect.

Lactobacillus shows anti-cancer activities. *L. plantarum* up-regulates the expression of *PTEN*, *Bax*, and *TLR4* and down-regulates the *AKT* genes, and then promote the apoptosis of AGS cells[64]. In *in vitro* studies, *L. gasseri* causes a significant decrease in the expression of oncogenes including *Bcl-2*, β -catenin, integrin $\alpha 5$, and integrin $\beta 1$. Overall, current evidence supports the notion that certain strains of *Lactobacillus* provide benefits for the human stomach through their properties of pathogen exclusion, maintaining the gastric barrier function, anti-inflammation, and anti-cancer effects.

Carcinogenic potentials of *Lactobacillus*

It is widely recognized that *Lactobacillus* has probiotic effects, which is capable of benefiting the human health at an adequate quantity. Recently, however, data supporting the bacterium occasionally shows carcinogenic potentials. In an INS-GAS transgenic mouse model, colonization with artificial microbiota (*L. murinus* ASF361, *Clostridium* ASF356, and *Bacteroides* ASF519) could promote the development of gastric intraepithelial neoplasia[12]. This is associated with a strong upregulation of pro-inflammatory genes and oncogenes[12]. These findings suggest a potential role of *Lactobacillus* in gastric carcinogenesis. *Lactobacillus* produces lactate, which may serve as a fuel for the tumor cells, accelerating their growth[15]. In a need of rapid growth, tumor cells rely primarily on anerobic glycolysis rather than oxidative phosphorylation, which provides more lactic acid[65,66]. The lactate concentration in glycolytic tumors is approximately 10 times higher than the basal lactate production in an average human[67-70]. It has been assumed that an increased production of lactic acid by *Lactobacillus* promotes the growth of tumor cells. Furthermore, *Lactobacillus* has been shown to reduce nitrate to nitrite, which leads to the formation of large amounts of N-nitroso compounds[71,72]. These compounds promote mutagenesis, angiogenesis, and protooncogene expression by epithelial cells, thus leading to the occurrence of GC. *Lactobacillus*, like other lactic acid bacteria, is a very potent inducer of reactive oxygen species in cultured cells and *in vivo*[73]. These reactive oxygen species induce intensively DNA damages[73]. It has been shown that lactic acid bacteria enhance the expression of NANOG, a known multipotency marker, turning human adult fibroblasts into multipotent cells[74]. This supports a direct cancer promoting activity of *Lactobacillus*.

RELATIONSHIP BETWEEN *LACTOBACILLUS* OVERGROWTH AND GASTRIC CARCINOGENESIS

Molecular analyses of the gastric microbiome have demonstrated overgrowth of *Lactobacillus* in GC. Recently, overgrowth of the bacterium has been found in cervical cancer[75]. *L. iners* was more abundant in cervical cancer and precancerous lesions. Similarly, some species of *Lactobacillus* have been found to have an increased abundance in GC[21]. These data suggest a close association between *Lactobacillus* and cancer. Considering that foods and drugs containing strains of *Lactobacillus* are widely

used in daily life and clinical settings, it is of immense importance to clarify whether overgrowth of *Lactobacillus* participates in the development of GC.

The genus *Lactobacillus* consists of more than 100 species. The biological behaviors vary substantially among different species. For instances, certain *Lactobacillus* strains possess urease activity which facilitates the inhibition of acidic environments of the stomach. In the normal human stomach, in contrast to that of mice, *Lactobacillus* was barely isolated [76,77]. To clarify the role of *Lactobacillus* in gastric carcinogenesis, a key issue remains to be resolved is whether the increased abundance of *Lactobacillus* detected by molecular analyses results from the overgrowth of a particular species of *Lactobacillus*. Results of preliminary studies, however, found that a diverse species of *Lactobacillus* have been isolated from the stomach of patients with GC [78-81]. These species include *L. paracasei*, *L. fermentum*, *L. rhamosus*, *L. salivarius*, *L. delbreuckii*, and *L. acidophilus*. These findings suggest that a great number of *Lactobacillus* species are capable of surviving and proliferating in the cancerous stomach. Although *Lactobacillus* was more frequently isolated from GC compared with non-cancer conditions, non-particular species has been found to be associated with GC [78-81]. Therefore, it appears that the overgrowth of *Lactobacillus* in GC is not caused by a particular species. Biological roles of *Lactobacillus* vary greatly among strains, no matter which species it is. Further studies are required to elucidate whether virulent strains, which have increased carcinogenic potentials mentioned above, are enriched in GC. Such studies would be beneficial for clarifying the role of *Lactobacillus* in GC.

Interactions between bacteria play a vital role in maintaining homeostasis of the microbiome. The co-occurrence network analyses demonstrate that *Lactobacillus* interacts with other bacterial members of the gastric microbiome [10]. Thus, overgrowth of *Lactobacillus* may alter the structure of the gastric microbiome through interactions with other bacteria, possibly leading to dysbiosis. This results in changes in the community behaviors, which enhance the carcinogenic potentials of the gastric microbiome. Thus, it is likely that *Lactobacillus* itself does not play any significant role in the carcinogenesis. Instead, it indirectly promotes carcinogenesis through altering the gastric microbial community. Bacterial overgrowth is commonly found in GC [13]. Overgrowth of *Lactobacillus*, thus, may merely reflect an altered state of the gastric microbiome that has many overgrown bacterial members. That is, the overgrowth of *Lactobacillus* plays little, if any, roles in the development of GC.

CONCLUSION

In summary, there is strong evidence supporting *Lactobacillus* overgrowth in GC. It may promote the development of GC directly through metabolic products, or indirectly through altering the microbial community. However, the possibility that it just acts as a marker for bacterial overgrowth cannot be excluded. To clarify the role of *Lactobacillus* in the development of GC, further studies at strain and species levels are indicated.

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