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TOPIC HIGHLIGHT

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Probiotics against neoplastic transformation of gastric mucosa: Effects on cell proliferation and polyamine metabolism

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Abstract

Gastric cancer is still the second leading cause of cancer death worldwide, accounting for about 10% of newly diagnosed neoplasms. In the last decades, an emerging role has been attributed to the relations between the intestinal microbiota and the onset of both gastrointestinal and non-gastrointestinal neoplasms. Thus, exogenous microbial administration of peculiar bacterial strains (probiotics) has been suggested as having a profound influence on multiple processes associated with a change in cancer risk. The internationally accepted definition of probiotics is live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. The possible effects on the gastrointestinal tract following probiotic administration have been investigated *in vitro* and in animal models, as well as in healthy volunteers and in patients suffering from different human gastrointestinal diseases. Although several evidences are available on the use of probiotics against the carcinogen *Helicobacter pylori*, little is still known about the potential cross-interactions among probiotics, the composition and quality of intestinal flora and the neoplastic transformation of gastric mucosa. In this connection, a significant role in cell proliferation is played by polyamines (putrescine, spermidine, and spermine). These small amines are required in both pre-neoplastic and neoplastic tissue to sustain the cell growth and the evidences here provided suggest that probiotics may act as antineoplastic agents in the stomach by affecting also the polyamine content and functions. This review will summarize data on the most widely recognized effects of probiotics against neoplastic transformation of gastric mucosa and in particular on their ability in modulating cell proliferation, paying attention to the polyamine metabolism.

Key words: Cell proliferation; Gastric cancer; Microbiota; Polyamines; Probiotics

Core tip: Studies linking probiotics and gastric neoplasms have mainly been addressed to evaluate the potential of probiotics as alternative regimen against *Helicobacter pylori*, a carcinogen tightly connected to gastric cancer. The effects of probiotics on gastric cell proliferation are still under investigation and interest has also been paid on the polyamines metabolism. Polyamines (putrescine, spermidine and spermine) are pivotal in regulating different metabolic functions, including cell proliferation. In this review, the authors try to summarize data on gastric cancer and the proposed abilities by probiotics in affecting the gastric integrity and cell proliferation, also in relation to the polyamine metabolism.

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INTRODUCTION

In spite of the significant reduction in its incidence and mortality in the last four decades[1], gastric cancer (GC) remains the second leading cause of cancer death worldwide, accounting for about 10% of newly diagnosed neoplasms[2].

In the last years, an emerging role has been attributed to the possible connections between the gastrointestinal (GI) content and the onset of neoplasms[3]. In this framework, modifications in the composition and quality of intestinal flora have been considered as having a deep impact on the host activities, not only at a local level on the different intestinal metabolic traits, but also in a more systemic fashion (*e.g.*, by affecting the immune response or cell proliferation)[4]. Thus, administration of peculiar positive bacterial strains (probiotics) has been suggested as having a profound influence on multiple processes associated with a change in cancer risk[5].

Many different definitions for probiotics have been proposed over the years. A widely accepted definition for probiotics is "mono or mixed cultures of live microorganisms which when administered in adequate amounts confer a health benefit on the host"[6]. Among them, lactic acid bacteria (LAB) and bifidobacteria are the most common types of microbes used[7]. To be metabolically active, these probiotic strains must survive passage through the GI tract, especially in the hostile gastric environment and resist to the enzymes of pancreas and bile acids. In this way they can reach the large intestine where they should be in sufficient amount to colonize mucosa and stools[8]. Besides, as stated by the international guidelines[9], for a reliable therapeutic use in humans, probiotics should be of human origin, safe for the host, and genetically stable.

The possible association between probiotics and GI neoplasms has mainly been evaluated in relation to colorectal cancer (CRC)[10].

In the stomach, studies linking probiotics and gastric neoplasms have been essentially addressed to evaluate the potential of probiotics as alternative regimen to eradicate *Helicobacter pylori* (*H. pylori*), a recognized carcinogen tightly connected to GC onset[11]. However, little is still known about the potential interactions between different strains of probiotics and the neoplastic transformation of gastric mucosa. In particular, the effects of probiotics on gastric cell proliferation are still under investigation and interest has also been paid on the polyamines metabolism. Putrescine, spermidine, and spermine are ubiquitous short-chain aliphatic amines involved in the regulation of cell proliferation and differentiation[12]. Polyamines can be considered reliable markers of proliferation since abnormal hyper-proliferative cells, such as in neoplastic and preneoplastic tissue, exhibit very high requirements for these amines to sustain cell growth through elevated DNA, RNA, and protein synthesis[13].

In this framework, this review will summarize data on gastric microbiota, the onset of GC and the proposed mechanisms of probiotics in contrasting the neoplastic transformation of the gastric mucosa. Additionally, attention will be focused on the possible influence of different probiotic strains on the polyamine metabolism.

HUMAN GASTRIC MICROBIOTA

The adult human GI tract contains 100 trillion microbial organisms, collectively denominated microbiota[14]. This microbe population is known to be dominated by strict anaerobes, including *Bacteroides*, *Eubacterium*, *Bifidobacterium*, *Fusobacterium*, *Peptostreptococcus*, and *Atopobium*. Anaerobic bacteria prevail aerobic bacteria by a factor of 100 to 1000 to 1 and include lactobacilli, enterococci, streptococci and *Enterobacteriaceae*. More than 500 different bacterial species have been described in the normal commensal microbiota, although the exact number and the variability among individuals are still object of deep investigations[15,16]. As reported in Figure 1, the bacterial density progressively increases along the proximal to distal segments of the GI tract and rises up to 10^{11} to 10^{12} bacteria per gram of colonic content[17].

The stomach is the least populated region of the GI tract (along with the esophagus and duodenum) and its microbial density ranges from 10 to 1000 CFU/g. Physiologically, this low number of bacteria in the gastric lumen has to be ascribed not only to low pH values, but also to rapid peristalsis and high bile concentrations. Different bacteria can regularly be sampled from the stomachs of healthy adults. Commonly detected phyla include Firmicutes, Actinobacteria, Bacteroidetes, and Proteobacteria, and characteristic genera are *Lactobacillus*, *Streptococcus*, and *Propionibacterium*[18].

The discovery of the spiral-shaped Gram-negative *H. pylori* inverted the conventional dogma of the stomach as a sterile organ. Actually, the stomach is populated by different bacteria and *H. pylori* is able to profoundly affect gastric physiology and the properties of the gastric mucosa as an ecological niche for other microbes[19]. As a result, the composition of the microbial population in the stomach may vary according to the presence or not of *H. pylori*.

Andersson *et al*[20] investigated the mucosa-associated microbiota of six healthy stomachs in a culture-independent study based on short 16S rRNA gene sequence reads by 454 pyrosequencing technology. Three of the six study subjects were not infected by *H. pylori*. The composition of their stomach microbiota was different from individual to individual, and only 33 out of the 262 phylotypes found were contemporary detected in all three samples. The authors hypothesized that the most abundant of the phylotypes found were apparently swallowed organisms originating from the mouth or esophagus. However, they also identified 177 phylotypes that were found in *H. pylori*-free stomachs, but not in the throat

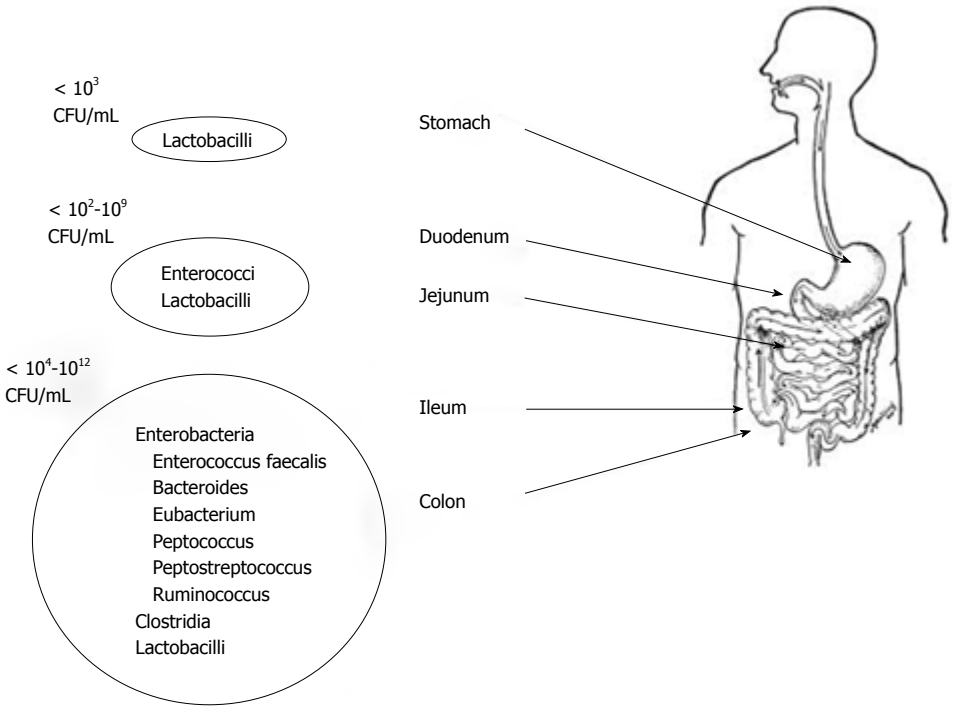

Figure 1 Bacterial composition and density along the proximal to distal segments of the gastrointestinal tract.

samples of other subjects participating the same study. While the most abundant phyla in the *H. pylori*-free stomachs were Actinobacteria, Firmicutes, and Bacteroidetes, the majority of the phylotypes that were not also found in throat samples, were identified as Proteobacteria.

In 2006, Bik *et al*[21] using a 16S rRNA clone library, described a large bacterial diversity in gastric biopsies from 23 esophagogastroduodenoscopies. Over 50% of the identified bacteria were classified as uncultivated, 10% of the phylotypes were previously uncharacterized. Overall, five major phyla (Proteobacteria, Firmicutes, Bacteroidetes, Actinobacteria, Fusobacteria) composed the bacterial diversity of the stomach. The authors reported results significantly different from those obtained in studies performed on the oral cavity and esophagus and this evidence allowed them to hypothesize a separate microbial ecosystem in the stomach. Interestingly, in that study the presence of *H. pylori*, gastric anatomical location and gastric pH value had no significant effects on the composition of the gastric bacterial population.

As the pathogen microbes concerns, the hostile environment of the human stomach can be colonized by other bacterial strains able to survive in those harsh conditions and other *Helicobacter* species with typical spiral morphology have also been found to be associated with gastric lesions and cancer. The percentage of patients infected with these "non-*H. pylori* helicobacters" (NHPH), previously denominated "*Helicobacter heilmanni*", is much lower than for *H. pylori*, varying between 0.2% and 6%[22]. Several studies have investigated the association between NHPH and human disease, including Crohn's disease, lithiasis, liver disease, coronary disease, gastritis, and pyoderma gangrenosum-like ulcers[23]. In addition to NHPH, other pathogen bacteria in the stomach may influence *H. pylori*-associated gastric pathogenesis by creating reactive oxygen and nitrogen species and modulating inflammatory responses. Non-*H. pylori* bacteria and their by-products may represent a persistent antigenic stimulus, thus increasing the inflammatory response induced by *H. pylori* infection[24].

A recent study by Hu *et al*[25] described a high prevalence (65.0%) of the non-*H. pylori* bacterial flora in the *H. pylori* positive patients, which indicated that the upper GI disorders may enable non-*Helicobacter* bacteria to survive and colonize the human stomach. The majority of these species were *Streptococcus*, *Neisseria*, *Rothia* and *Staphylococcus*, differing in composition compared to *H. pylori* non infected patients. Considering that not all the bacterial species can be cultivated due to the harsh culture condition, the number of these non-*H. pylori* pathogenic bacteria may be higher than that found.

GASTRIC CANCER

GC represents the second cause of cancer-related death worldwide, accounting for nearly 11% of cancers in males and 7% in females[26]. The GC incidence varies between populations with huge fluctuations. In Japan, the incidence is 80 per 100000 males, while in Africa the overall incidence is only 5 per 100000. In Europe, the incidence rates range from 20 to 40 per 100000[26]. In Italy, GC represents the fourth most common cancer (following lung, breast, and colorectal cancer) and its incidence yields its peak during the seven decade of life, being rare in patients younger than 40 years. Besides, the mortality in Northern and Centre regions is twofold higher than

that in Southern Italy[27].

The development of GC is a multi-step process (Correa's hypothesis) on which many individual and environmental factors contribute[28]. The most known and debated cause of GC is the presence of *H. pylori* infection. The International Agency for Research on Cancer classified *H. pylori* as a Group 1 human carcinogen. This is still the most important single risk factor for GC present in almost 50% of world population[29] and causally correlated with chronic gastritis, peptic ulcer, gastric atrophy and gastric lymphoma other than GC[30,31].

Evidences supporting the pivotal role of *H. pylori* infection in the gastric neoplastic transformation derive from studies on infected patients with mucosa associated lymphoid tissue (MALT)-lymphoma gastric tumors. After successful *H. pylori* eradication, these patients healed completely and both GC and tumor promoting proliferation of lymphoid tissue disappeared[32,33].

Low socio-economic status, *H. pylori* infection in family members living in crowded house-shelters and poor sanitation are the most favorable conditions for *H. pylori* transmission from person to person and cancer risk. In the last years, the overall GC incidence is constantly falling, possibly due to the fall in the *H. pylori* prevalence caused by increasing living standard level, but not in populations at high risk. Besides, the incidence of GC is decreasing in the distal stomach and increasing in the gastro esophageal junction[34].

Other environmental and dietary factors, tobacco use, achlorhidria and bacterial overgrowth can promote in gastric mucosa the pathways of cellular growth altering the growth/apoptosis balance[35]. The major dietary factors considered in relation to GC onset are salt ingestion, smoked foods, and frequent use of cooking oil. Previous studies showed that diets rich in these components significantly increase by two-fold the GC risk[36-38]. A possible explanation is that salt may damage the protective mucosal layer of the stomach. Besides, diets with high-salt content contribute to expansion of *H. pylori* colonization[39] and deep-oil-fried foods have been demonstrated to produce human carcinogens such as benzo[*a*]pyrene and dibenz[*a*,*h*]anthracene, and heterocyclic aromatic amines, due to high frying temperatures[40]. By opposite, a diet with fresh foods rich in vitamin C (including fresh foods, vegetables, and fruit) has been demonstrated to be protective. An antineoplastic role for vitamin C has been hypothesized[41] since this vitamin may prevent GC cell growth, probably by blocking the formation of human carcinogenic *N*-nitroso compounds, and significantly reducing the nitrite concentration by 43%[42]. Additionally, diets with a high content in green tea[43] or other substances with postulate antineoplastic activities such as whole grain cereals, garlic or vitamins, have also been associated with a reduced risk of this cancer[44], even if there is still uncertainty if changing diet habits to introduce more of the above cited compounds would effectively reduce the GC risk[45].

POTENTIAL OF PROBIOTICS TO PREVENT NEOPLASTIC TRANSFORMATION OF GASTRIC MUCOSA

It is estimated that 20% of malignancies worldwide can be attributed to infections and the classical example is provided by the association between *H. pylori* with both GC and MALT. More in general, the chronic alteration of intestinal microbiota homeostasis could promote many diseases, including cancer. The mechanisms by which bacteria may induce carcinogenesis include chronic inflammation, immune evasion, and immune suppression. Elevated numbers of T regulatory cells have been demonstrated to suppress the innate and adaptive immune responses, thereby contributing to tumor progression[46].

The complex interactions between diet, normal intestinal microbiota and health encouraged the development of strategies that allow for the selective growth of probiotics[47]. However, although *in vitro* and animal model studies suggest a protective anticancer effect of probiotics, the results of studies performed in humans are still controversial.

Therapeutically, there has been an increased interest on the use of probiotics for prevention and treatment of a number of GI disorders, including irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), pathogenic bacterial or viral infections, antibiotic associated diarrhea, and also as antineoplastic agents in colon[48,49]. By opposite, little attention has been paid to probiotics and GC. Theorically, probiotics might exert their action also in the gastric mucosa. In the normal stomach, LAB concentrations may vary between 0 and 1000/mL. Being acid resistant, they persist in the stomach longer than other bacteria: dietary strains of bifidobacteria and lactobacilli survive in high proportions (> 80%) in the gastric environment for periods of 2 h[50]. The majority of available data on their putative mechanism of action in the stomach derives from studies on the effects against the carcinogen *H. pylori* infection[51], but the etiological mechanisms are still far from being fully understood. In fact, the acidic gastric environment represents an effective barrier against many of the pathogen bacteria that reach the GI tract.

A change of the physiological conditions of the stomach, as it occurs in different diseases (corpus atrophy or GC itself) or during drug administration [*e.g.*, long term proton pump inhibitor (PPI) therapies], may provide a chance for extraneous microbes to colonize the stomach. Predominant gastritis of the corpus leads to atrophic gastritis with a low production of gastric acid (hypochlorhydria)[52]. The inhibition of normal gastric acid secretion is considered at increased risk of developing GC[53], since it bears important side effects. The most important is the possible significant reduction of the "gastric barrier effect" and the bacterial overgrowth in the stomach and duodenum with a concentration of > 100000 viable cells/mL. As a major consequence of

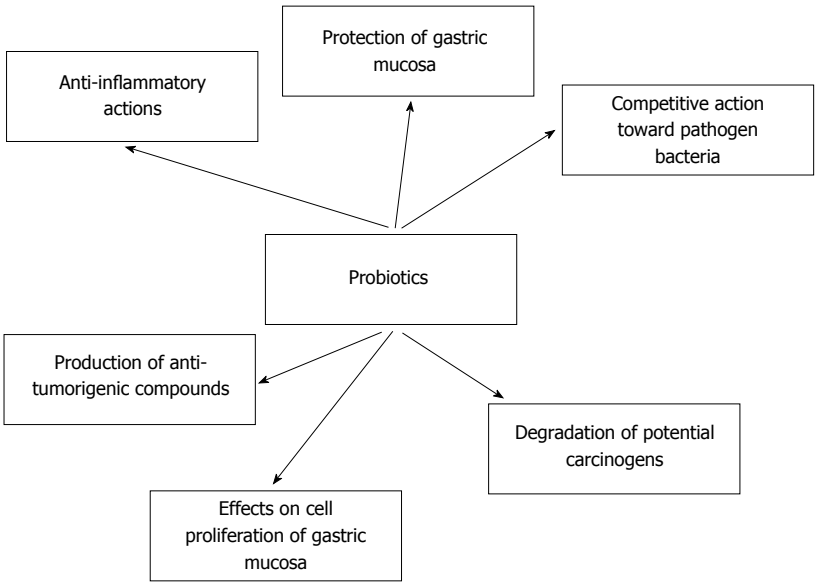

Figure 2 Proposed mechanisms of probiotic activities against gastric cancer.

Table 1 Possible mechanisms of protection of the gastric mucosal barrier induced by probiotics

Increased levels of basal mucosal prostaglandins
Increased cell proliferation/apoptosis ratio and stimulation of angiogenesis
Stimulation of local immune responses
Release of antioxidant substances
Stimulation of the expression of gastric mucins
Improvement in gastrointestinal permeability
Decreases in bacterial overgrowth

this condition, many harmful or even pathogenic bacteria contained in some foods could survive the gastric transit and colonize the stomach itself, the duodenum, or the gut, where they could establish acute and chronic infections. Some of these bacteria can reduce nitrogen and produce carcinogenic *N*-nitroso compounds through conversion of nitrates or nitrites from the saliva[54].

The possible mechanisms by which probiotics exert their effects against neoplastic transformation of the gastric mucosa concern: (1) the protection of mucosa and stabilization of the GI barrier function; (2) a competitive action toward pathogen bacteria; (3) degradation of potential carcinogens; (4) anti-inflammatory action; (5) production of anti-tumorigenic or anti-mutagenic compounds; and (6) the effects on cell proliferation and the polyamine metabolism of the gastric mucosa (Figure 2).

Protection of gastric mucosa and stabilization of the GI barrier function

Homeostasis in the stomach environment is maintained by the balance of protective and aggressive factors and drugs. An overload of aggressive factors (*e.g.*, gastric acid, stress, and alcohol) that upsets this balance can induce gastric injury.

The gastroduodenal microbiota, is low numerically, but could participate in the protection of the mucosa. Many factors may explain this protective activity and are summarized in Table 1.

It has been suggested that the protective action of probiotics on induced gastric mucosal lesions could be attributed to different factors such as prostaglandins, growth factors and cytokines. Also the regulation of cellular apoptosis, proliferation, gastric mucin production and GI permeability appears to be actively involved.

Increased levels of 6-ketoprostaglandin F1-α, epidermal growth factor (EGF) and b-fibroblast growth factor have been implicated in the protective effect displayed by peculiar bifidobacterial strains such as *Bifidobacterium brevis* (*B. brevis*)and *B. bifidum* against gastric ulceration induced by acetic acid or ethanol in rats[55]. Pre-treatment of rats with *Lactobacillus rhamnosus* GG (*L.* GG) at 10^9 CFU/mL twice daily for three consecutive days was able to markedly lessen the suppressive actions of ethanol on mucus-secreting layer and trans-mucosal resistance along with an increase in the basal mucosal prostaglandin E2 (PGE2) levels and a concomitant reduction of cellular apoptosis[56]. In a more recent study aimed at determining the role of viable lactobacilli in the healing of acetic acid-induced chronic gastric ulcer, Uchida *et al*[57] reported that a yogurt containing *L. gasseri* OLL 2716 inhibits the formation of HCl-induced acute gastric lesions through the generation of PGE2. Overall, these findings suggested that the up-regulation of prostaglandins could stimulate the mucus secretion and increase the transmucosal resistance in the gastric mucosa.

L. GG was also proven to enhance the healing of acetic acid-induced gastric ulcer in rats, *via* the attenuation of cell apoptosis to cell proliferation ratio accompanied by a significant ornithine decarboxylase (ODC) up-regulation and B-cell lymphoma 2 protein expression at the ulcer margin[58]. The phosphorylation level of EGF receptor was also up-regulated without altering the total EGF receptor expression. Angiogenesis was also signifi-

cantly stimulated together with the induction of vascular endothelial growth factor (VEGF) expression.

The role of VEGF was also investigated in a study testing the ability of the probiotic mixture VSL#3 (a combination of eight probiotic bacteria including *Lactobacilli*, *Bifidobacteria* and *Streptococcus* species) in healing acetic acid induced gastric ulcer in rats[59]. VSL#3 was administered orally at low or high dosages from day 3 after ulcer induction for two weeks. The gene expression of several pro-inflammatory cytokines, protein and expression of stomach mucin5ac (muc5ac), regulatory cytokine-IL-10, COX-2 and various growth factors were evaluated. Remarkably, the probiotic efficacy was effective at higher concentrations of VSL#3 by specifically increasing the expression and production of angiogenesis promoting growth factors, primarily VEGF that was dramatically increased after 7 d of treatment.

In another work performed on laboratory animals, Senol *et al*[60] demonstrated that the pretreatment with a probiotic mixture (13 different bacteria) attenuated the aspirin-induced gastric lesions by reducing the proinflammatory cytokines and the lipid peroxidation, enhancing mucosal sIgA production and stabilizing mucosal mast cell degranulation into the gastric mucosa.

Stimulation of the expression of gastric mucins appeared to be pivotal in the protective effects by probiotics against gastric injury. Gomi *et al*[61] investigated the properties of *B. bifidum* BF-1 in a rat model of acid-ethanol-induced acute gastric ulcer. The gastric lesions were proven to be significantly lower in the BF-1 group than in the control group, which showed a similar level to the group treated with another bacterium, the *Streptococcus thermophilus* YIT 2021 ST. The production of gastric mucin and the expression of several target genes associated with protection and inflammation were examined before and after induction of gastric injury. Muc5ac gene expression in gastric corpus samples and gastric mucin production in stomach samples from the BF-1 group were significantly higher than those in the respective samples from the control group. These findings indicated that BF-1 has the potential to provide gastro-protection, alleviating acute gastric injury by enhancing the production of gastric mucin in rats.

The importance of gastric microbiota in the protection against gastric lesions has been suggested by studies demonstrating that the alteration of homeostasis of the resident microbiota contributed to the development and persistence of injuries[62].

PPIs are commonly used to treat acid-related diseases, mainly gastroesophageal reflux disease. However, PPIs may indirectly affect the microenvironment of the flora *via* changes in pH[63]. Chronic PPI administration exposes the subject to the risk of exogenous infections as most pathogens are able to survive the gastric transit in a condition of significantly decreased acidity. In order to evaluate the ability of probiotics in preventing the "gastric barrier effect" from prolonged use of PPIs, different probiotic bacteria considered as having a strong inhibitory activity on gram-negative bacteria [*L. rhamnosus* LR06 (DSM 21981), *L. pentosus* LPS01 (DSM 21980), *L. plantarum* LP01 (LMG P-21021), and *L. delbrueckii* subsp. delbrueckii LDD01 (DSM 22106)], were tested on a group of 30 patients treated with PPIs for either short (3 to 12 mo) or long-terms (> 12 consecutive months) in comparison to a control group[64]. The total viable cells and total lactobacilli were quantified in gastric juice and duodenal brushing material from all subjects. As expected, the results confirmed the strong bacterial overgrowth in the stomach and duodenum of people treated with PPIs compared with subjects with a normal intragastric acidity. In addition, the bacterial cell counts in subjects who underwent a long-term treatment with a PPI were greater than those from subjects taking these drugs for short term. Total lactobacilli represented the major percentage of bacterial counts, thus demonstrating the ability of such bacteria to colonize the stomach and the duodenum, at least temporarily, and to consequently restore the gastric barrier effect.

Alterations in GI permeability are considered as an initial step in the development of gastric lesions such as ulcers. In a human study, Gotteland *et al*[65] demonstrated that intake of *L.* GG protects the gastric mucosa in healthy volunteers against alterations of permeability induced by the acute administration of non-steroidal anti-inflammatory drugs (NSAIDs), an important cause of gastroduodenal ulcer.

In a manner similar to that of *L.* GG, *L. gasseri* OLL2716 proved to protect the gastric mucosal permeability against aspirin using[66]. The urinary sucrose excretion (USE) test was carried out in 29 volunteers before and after probiotic treatment for 4 wk and 37 patients undergoing low-dose aspirin therapy who took *L. gasseri* OLL2716 for 16 wk. The authors found that in healthy volunteers the elevation in the USE value after aspirin loading significantly decreased after probiotic treatment. Interestingly, also in patients assuming aspirin, the USE value significantly decreased in the period with *L. gasseri* OLL2716 administration, while no significant difference was found in the period without probiotic.

Competitive action toward pathogen bacteria

Ability by probiotics to adhere to GI mucus is of considerable importance to exert a modulatory effect *in situ*, especially on the gastric mucosa surface. Probiotics can compete with and prevent establishment of pathogenic bacteria by competitive exclusion. Several studies that characterized different LAB strains have shown their ability to adhere to gastric epithelial cells *in vitro* and *in vivo*[67-69]. A wide selection of proteinaceous and nonproteinaceous surface components (lipoteichoic acids and specific structures such as external appendages covered by lectins)[70] have been demonstrated to be involved in adhesion to epithelial cells through different mechanisms, including hydrophobic and electrostatic interactions as well as passive or steric forces. In a recent paper, Chen *et al*[71] demonstrated the antagonistic activities of *L. gasseri*

Chen and *L. plantarum* 18 against *H. pylori* growth and infection. *H. pylori* adhesion to the human gastric epithelial cells SGC7901 was efficaciously inhibited by administration of the cell free supernatants and both live and dead lactobacilli. The growth of *H. pylori* in the gastric mucosa was also significantly inhibited by the administration of *L. johnsonii* MH-68 and *L. salivarius* ssp. salicinius AP-32, either alone or in combination[72].

Cui *et al*[73] isolated *L. fermenti* and *L. acidophilus* from human gastric mucosa and screened their potential anti-*H. pylori* activity and antinflammatory effects on a mouse model of *H. pylori*-associated Balb/c gastritis. The authors reported that these probiotic strains are able to adhere to gastric epithelium, exerting also a significant anti-*H. pylori* activity. Interestingly and with possible therapeutical implications, *L. fermenti* displayed *in vivo* a valid anti-*H. pylori* activity whose efficacy was almost similar to the standard triple therapy, thus significantly improving the *H. pylori* associated Balb/c gastritis.

Degradation of potential carcinogens

Among the functional properties characterizing probiotic strains, antigenotoxicity and antimutagenicity could be pivotal against cancer[74]. As demonstrated by epidemiological researches, LAB intake is related to a reduced GI neoplasm incidence[75] and experimental evidences have highlighted the ability of lactobacilli and bifidobacteria to inhibit carcinogen-induced tumor development, at least in the large intestine[76,77].

The theory of the "*luminal steady state*" suggests that the end products of carbohydrate metabolism in the intestine such as short chain fatty acids (SCFA), formic, acetic, propionic, butyric and lactic acids, may have a beneficial effect because they can act as colonic nutrients. These actions may be counteracted by the products deriving from the metabolism of proteins (phenolic compounds, amines, ammonia, *N*-nitroso compounds, and indoles) which might have detrimental effects on the host[78].

Heterocyclic aromatic amines (HCA) are compounds with high mutagenic potential, formed during the cooking of meats at high temperatures of 150-300 ℃. Numerous studies have shown that these amines are involved in the etiology of gastric and colon cancer in humans. The inactivation of HCA by LAB has been reported in several articles and studies performed *in vitro* and laboratory animals have demonstrated that probiotic bacteria prevent induction of DNA-damage and preneoplastic lesions induced by certain HCA[79,80].

Stidl *et al*[81] conducted a comprehensive investigation on the ability in inactivating HCA by different LAB species present in fermented foods or derived from the human GI tract. In their paper, the authors proved the existence of clear differences in the binding behavior of LAB towards structurally different amines. Different physicochemical properties of the amines such as the pKa-values, solubility and lipophilicity may affect their elimination by LAB. Besides and in agreement with earlier investigations[82], the experiments on bacterial mutagenicity showed that the inactivation of the amines by LAB induces a decrease of their mutagenic potential, correlating also with the binding capacities of the individual probiotic strains.

Antinflammatory action

Probiotics significantly affect the innate as well as the acquired immune system by different products such as dead cells, metabolites, parts of the cell wall, and DNA. All these components are recognized by host cells equipped with appropriated receptors. In this context, the main target is represented by epithelial and gut-associated immune cells.

A signaling cascade leading to immune modulation may be triggered by the adhesion of probiotics or their components to epithelial cells as well as the release of soluble factors. These probiotic actions could be important for the suppression of neoplastic host cells[83].

Also in this case, the main trigger for eliciting the immune cells in the stomach is represented by *H. pylori* infection. One of the well-known carcinogenesis pathways related to *H. pylori* is through the sequence "inflammation-atrophy-intestinal metaplasia-dysplasia-adenocarcinoma"[28].

The efficacy of probiotics in the treatment of inflammation-based GI diseases is both founded on the inhibition of pathogenic bacteria and inflammatory processes[84].

Lee *et al*[85] found that the enhancement of antinflammatory signals might be essential mechanisms of probiotics rather than attenuating inflammatory signals imposed by *H. pylori* infection. In their study performed on AGS cell line, the authors found that *H. pylori* or its lipopolysaccharide stimulation were able to significant increase expressions of different inflammatory mediators (*e.g.,* TNF-α, IL-8, inducible NOS and COX-2). Pretreatment of cells with *L. plantarum*, *L. rhamnosus* and *L. acidophilus* significantly inhibited these mediators. The authors postulated that these antinflammatory effects were obtained by enhancing the expression and signaling of suppressor of cytokine signaling 2 and 3 (SOCS-2 and SOCS-3). Their expression is mediated through both significant phosphorylation of signal transducers and activation of transcription (STAT)-1 and STAT-3, and simultaneous inhibition of Janus kinase (JAK)2 phosphorylation, which is known to signal SOCS-2/SOCS-3 negatively[86,87].

H. pylori can induce TNF-α and IL-8 pro-inflammatory cytokine expressions in MKN45 cells. Pretreatment with *L. acidophilus* counteracted *H. pylori*-induced IL-8 expressions, specifically by mediation through the IκBα/NF-κB pathway in a dose-dependent manner. Moreover, *L. acidophilus* ameliorated IFN-γ-induced Smad7 translation level and improved the *H. pylori*-induced gastric inflammation *in vitro*[88]. Besides, in "*in vivo*" studies, the *H. pylori*-infected gastric mucosa showed up-regulated NF-κB pathway and Th1 type cytokine responses[89,90], which may disturb the integrity of the gut epithelial barrier.

Administration of *L. rhamnosus* R0011 and *L. acidophilus* R0052 after infection eradicated *H. pylori* and reversed gastric inflammation in laboratory animals[91]. Similar results were reported with *L. gasseri* OLL2716[92].

Production of anti-tumorigenic or anti-mutagenic compounds

The effect of probiotics can be due to the production of different antimicrobial compounds and the two main categories are SCFAs and bacteriocins.

SCFAs are produced during the metabolism of carbohydrates by probiotics and have an important role in physiological functions. Since they derive from carbohydrates, these anions may be modulated by the dietary modifications. SCFAs were shown to play a key role in modulation of the digestive epithelial cells proliferation/apoptosis balance. This involves stimulation of differentiation in healthy cells, nuclear receptor activity through mitogen-activated protein kinase activation, histone deacetylase inhibition and apoptosis stimulation in transformed cells[93].

Apoptosis is a natural physiological process that regulates the number of cells and represents an ideal target for anti-neoplastic strategies. Through a series of regulated processes, cancer cells become fragmented and their residual portions are absorbed by adjacent tissues and immune system[94].

In human gastric carcinoma cell lines, both butyrate and propionate have been found to be able to induce apoptosis[95]. Two main apoptotic pathways are involved: the extrinsic pathway, mediated by activation of caspase 8 and death receptors and the intrinsic pathway, in which a role is played by caspase 9 and mitochondria[85].

It is postulated that cancer cells generally lack for apoptotic control, and hence their proliferation is constantly fostered. Therefore, the ability to induce apoptosis of cancer cells shown by different LAB may reflect an intrinsic anti-neoplastic potential. In this connection, dairy propionibacteria have been proven to produce beneficial pro-apoptotic SCFAs, hence they may be useful in cancer prevention or treatment[96].

SCFAs may also act against *H. pylori* infection. Bhatia *et al*[97] were the first to report an antagonistic action of *L. acidophilus* against *H. pylori* and to hypothesize a role for SCFAs in this effect. The reported antimicrobial activity could be due not only to a direct competition with *H. pylori*, but also to the inhibition of its urease activity, as shown with two high lactic acid producers, namely *L. salivarius* and *L. casei Shirota*[98,99].

The establishment in the stomach mucosa by probiotics is hampered by hostile conditions. Thus, administration of positive bacterial strains in combination with prebiotics (synbiotic) may facilitate their settlement and enhance their properties. Prebiotics are defined as non-digestible food ingredient able to selectively stimulate their growth and/or activity[100] and different papers have highlighted this ability, at least in the colonic lumen. Use of probiotic bacteria with oligosaccharides could promote bacterial growth and increase great quantities of butyrate, which has been shown to have antitumor effects at the cell level[48]. Rodent studies demonstrated that a synbiotic combination of resistant starch and *B. lactis* exerted a pro-apoptotic action in response to the carcinogen azoxymethane[101].

Another class of substances with a reported antimicrobial and antineoplastic activity is represented by bacteriocins. These small, heat resistant and dialyzable peptidic structures possess a spectrum of antimicrobial activity against closely related Gram positive and Gram negative pathogens, including food-borne pathogens[102].

Not all the bacteriocins show the same inhibitory activity. *L. salivarius* UCC118 produces a peptide that inhibits different pathogens such as *Bacillus*, *Staphylococcus*, *Enterococcus*, *Listeria*, and *Salmonella* species[103]. Lacticin 3147, a bacteriocin produced by a *Lactococcus lactis* strain, has shown the ability to inhibit a range of genetically distinct *Clostridium difficile* isolated from healthy subjects as well as patients with IBD[104].

Different lactobacilli have been demonstrated to produce these peptidic structures in the stomach. However, other probiotic strains such as *Enteroccus faecium*[105], *Bacillus subtilis*[106] and *Bifidobacterium*[107] could also produce heat-stable proteinaceous compounds capable of inhibiting *H. pylori* growth.

LAB strains can also produce a wide range of substances other than bacteriocins acting in a positive fashion for the gastric environment. Among them, the exopolysaccharides, polymeric substances that promote the colonization of probiotic bacteria by cell to cell interactions in the alimentary tract. Additionally, biosurfactants have shown to reduce adhesion of pathogens into gastric wall membrane due to their antiadhesive properties. LAB strains have also been reported for production of antioxidants that scavenge the free radicals such as superoxide anions and hydroxyl radicals[108].

As concerns the suggested antioxidant activities, a possible therapeutic use of synbiotic was investigated by Singh *et al*[109]. The authors evaluated the effects of a novel combination of *L. acidophilus* together with ginger extract, a bioactive phytochemical with antioxidant and antiulcer effects. This synbiotic formulation was administered to rats in a form of floating beads and demonstrated to reduce the oxidative stress and be effective in terms of ulcer index, mucus secretion, and histopathological parameters in comparison to control animals. This approach could be interesting for the management of gastric diseases since the use of probiotics is limited due to their transience and inability to survive the adverse physiological conditions of the GI tract. Therefore, packaging probiotics and prebiotics in a suitably pharmaceutical formulation may facilitate their establishment in the stomach mucosa.

Effects on the polyamine metabolism and cell proliferation of the gastric mucosa

Beyond the production of specific bacterial enzymes,

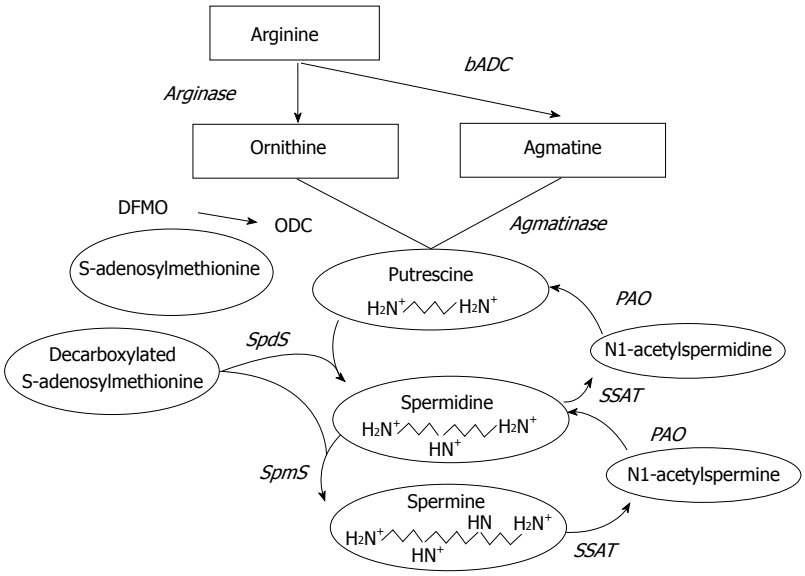

Figure 3 Schematic depiction of the polyamine metabolism. ODC: Ornithine decarboxylase; PAO: Polyamine oxidase; SSAT: Spermidine-spermine-*N*-acetyl transferase.

reactive oxygen species, and effects on the host metabolome, the mechanisms by which probiotics inhibit cancer development may involve multiple pathways, including the regulation of cell proliferation and the apoptotic processes[110]. Such anti-carcinogenic properties have also been studied at a molecular level[111] and by analysis of intermediate biomarkers of proliferation such as polyamines (putrescine, spermidine and spermine)[112]. These small molecular weight amines are highly required in both pre-neoplastic and neoplastic tissue to sustain the enhanced cell growth[113].

Polyamine synthesis is an early event occurring during the G1 phase of the cell cycle and represents a requisite for proliferating cells to start their processes. Their metabolism begins with the intervention of the rate limiting enzyme ODC that is finely tuned in all of the proliferating cells and is subjected to different growth promoting stimuli[114].

Figure 3 shows a schematic representation of the polyamine metabolic pathway. Briefly, biosynthesis is mediated by the key enzyme ODC which converts the amino acid ornithine into putrescine. This is then sequentially converted into spermidine and spermine through the action of the enzyme S-adenosylmethionine decarboxylase and spermidine/spermine synthase. The central enzyme in the polyamine catabolic pathway is the spermidine-spermine-*N*-acetyl transferase, which adds acetyl groups to terminal amine groups in spermidine and spermine. These acetylated polyamines are then substrates for the enzyme polyamine oxidase (PAO) which retro-converts these acetylated derivatives into lower chain amines.

Polyamine concentrations increase during carcinogenesis and an increase in ODC activity accompanies neoplastic transformation of the mucosa[115]. As with other tumors, the content of polyamines in GC is higher compared to the adjacent mucosa and equivalent normal tissue[116]. In the stomach, polyamines are also increased in pre-neoplastic conditions such as during *H. pylori* infection. Polyamines were evaluated in antral and body biopsies of 26 dyspeptic patients (20 *H. pylori* positive and 6 *H. pylori* negative) undergoing gastroscopy[117]. Antral and body biopsies from infected patients contained higher polyamine levels than those from non-infected subjects. In *H. pylori* positive patients, the baseline polyamine levels were higher in the antrum than in the body, whereas levels in the two stomach regions were similar in *H. pylori* negative subjects. After therapy, polyamine levels decreased in patients with successful eradication, but they remained unchanged in patients in whom infection persisted.

The increase in the polyamine content seems to be due to the loss in polyamine homeostasis occurring during the dysregulation of cell proliferation. This is also proven by evidences of an up-regulation of polyamine biosynthesis, a decrease in their catabolism, and an increased uptake[115].

Since polyamines and their enzymes are strongly related to neoplastic proliferation in the GI tract, all the strategies of interventions targeting polyamines, including probiotics, deserve deep investigations.

Our group[118,119] found that *L.* GG administration induced a significant reduction in polyamine biosynthesis in two different human GI cancer cell lines, one originating from undifferentiated carcinoma of the stomach (HGC-27), the other from colon adenocarcinoma (DLD-1). Interestingly, when the cytoplasmic extract derived from *L.* GG homogenate was tested, the cytoplasmic extract, but not the cell wall extract, was shown to be suppressive.

In an *in vivo* study, Linsalata *et al*[120] demonstrated that the ingestion of VSL#3 reduced polyamine levels and ODC activity in colorectal mucosa of rats. Besides,

in a human study by the same group, a peculiar *L. brevis* strain CD2 demonstrated anti-proliferative biochemical features[121]. In this study, a cohort of *H. pylori*-positive dyspeptic patients randomly received high oral doses of *L. brevis* CD2 or placebo, for 3 wk before endoscopy. Before and after treatment, *H. pylori* infection was determined by urea breath test. In gastric biopsies, ODC activity and polyamine levels were evaluated by a radiometric technique and high-pressure liquid chromatography, respectively. The study demonstrated that administration of *L. brevis* CD2 alone did not eradicate *H. pylori* even if a reduction in the UBT delta values occurred, suggesting a decrease in intragastric bacterial load. Significantly, *L. brevis* CD2 induced a decrease in gastric ODC activity and polyamine levels. These data support the hypothesis that *L. brevis* CD2 treatment can decrease *H. pylori* colonization, thus reducing polyamine biosynthesis. Probably, the arginine deiminase activity following the probiotic treatment might cause arginine deficiency, preventing polyamine generation from gastric cells. This enzyme induces the catabolism of arginine and can affect the biosynthesis of polyamines[122]. In this connection, in a study performed on the human T leukemia Jurkat cell line, Di Marzio *et al*[123] demonstrated that lyophilized and sonicated preparations of *L. brevis* CD2 were able not only to cause arginine-dependent polyamine synthesis inhibition, but also to induce consequently a relevant apoptotic effect.

The rates of cell proliferation and apoptosis may determine the speed of neoplastic growth[124]. Apoptosis is frequently impaired in many human tumors and is also an important phenomenon in chemotherapy-induced tumor cell death. Therefore, the modulation of apoptosis has been hypothesized as an effective technique in the treatment of cancer[125]. As postulated in the colonic environment, the induction of apoptotic processes by gut microbiota could represent the so-called physiologic "oncologic surveillance" mechanism for the proliferative disease prevention[126], but this hypothesis waits for further testing before confirmation in the gastric environment. It has been demonstrated that the antiproliferative effect and the induction of apoptosis caused by two lactobacillus strains (*L. paracasei* IMPC2.1 and *L.* GG) were quite similar in both HGC-27 and DLD-1 cancer cell lines and they were mediated not only by live microorganisms but also nonviable ones[118].

A milk fermented by *Propionibacterium freudenreichii* was recently tested for its pro-apoptotic potential on HGT-1 human GC cells. Fermented milk supernatant induced typical features of apoptosis including chromatin condensation, formation of apoptotic bodies, caspase activation and cytochrome c release, DNA laddering, cell cycle arrest, and reactive oxygen species accumulation. Moreover, this fermented milk enhanced the cytotoxicity of camptothecin, a drug used in GC chemotherapy. This kind of functional foods may represent a useful tool as part of a preventive diet designed for GC prevention and/or as a food supplement to potentiate cancer therapeutic treatments[127].

The proliferation and cell death of KATO3 cells, a GC cell line, were examined after treatment with *L. casei* extract for various times and at various doses. *L. casei* extract inhibited the growth of KATO3 cells and induced apoptosis by inactivating NF-κB promoter activity. However, apoptosis induced by *L. casei* extract was not directly associated with the intrinsic mitochondrial pathway. Immunoblot analysis revealed that *L. casei* extract decreased the expressions of NF-κB and IκB. The reduced NF-κB levels led to a concomitant decreased phosphorylation of mTOR signaling components, such as PI3K, Akt, and p70S6 kinase[128].

Other mechanisms of action may be evoked. The anti-proliferative capabilities of probiotics may be related to their previously described ability to adhere to cells. Lee *et al*[129] found that *Bacillus polyfermenticus* SCD was strongly adherent to Caco-2 cells and inhibited the growth of colon cancer cells in a dose dependent manner.

Bacterial enzyme inhibition and anticancer activity of *B. adolescentis* SPM0212 was assessed in three human colon cancer cell lines: HT-29, SW-480, and Caco-2. Cell proliferation was inhibited in all the cancer cell lines. Besides, this probiotic strain inhibited in a dose-dependent fashion TNF-α production as well as modifications in cellular morphology. Finally, this bacterial strain was proven to hinder harmful fecal enzymes, including beta-glucuronidase, beta-glucosidase, tryptophanase, and urease[130].

CONCLUSION

There is a growing body of evidence that different microbes may contribute to gastric tumorigenesis and exogenous administration of probiotic bacteria may be of some help in preventing/contrasting neoplastic transformation of the gastric mucosa. In this context, not only dietary modifications or drugs can affect the numbers and types of microorganisms in the stomach, but microorganisms can also generate *per se* new compounds from food components, some of which can be beneficial while others may be harmful.

LAB and Bifidobacteria are the most common types of microbes used as probiotics, and are also considered as markers of stability of the normal human intestinal microbiota. Against a huge amount of data suggesting a role for probiotics in CRC prevention, few investigations are available on their effects on GC. Despite this, probiotic strains have been proven to be helpful, at least in the management of a gastric pre-neoplastic condition such as *H. pylori* infection[103]. One suggested mechanism related to probiotic therapy is that these microbes can adhere and even transiently reside in the stomach, enhance the immune response, and reduce the *H. pylori* inflammation effect on the host gastric mucosa[131]. Notwithstanding, the *in vitro* and *in vivo* data here reported suggest a role for probiotics also in controlling the rate of proliferation of neoplastic cells in human GC cell lines as well as in animal stomachs. Therefore, many of these bacteria, together with microbially generated metabolites, may have a role in

GC risk or development. Nonetheless, there are still unanswered questions. Who might benefit from dietary interventions to alter their indigenous microbe population? How does individual's genetic background influences their microbiota? What are the active metabolites of food components? Can we identify inter-individual variability in the production of these substances? How can these substances be better utilized for cancer prevention?

Only when an answer for each of these questions will be available, it will become possible to develop a more specific strategy for preventing or, at least, delaying the onset of neoplastic transformation of the gastric mucosa based on precise modifications of the composition or activities of the GI microbiota.

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