7 Potential Correlation Between Homeostasis Control and Tumor Microenvironment Regulation of Probiotic as a Therapeutic Agent to Manage Gastrointestinal Cancer

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Abstract

Gastrointestinal (GI) cancer possesses a serious global public health problem. GI cancer refers to a group of cancer that affects various parts of digestive system that includes gastric cancer (GC), colorectal cancer (CRC), hepatocellular carcinoma (HCC), esophageal cancer (EC), and pancreatic cancer (PC). As compared to other cancer cases, GI cancer accounts 25% of all cancers and causes almost 9% of all cancer related deaths worldwide. The human intestinal microbiota interacts with host and influences a plethora of activities, such as metabolism, nutrient absorption, provides resistance against pathogenic microorganisms, and also plays an important role in the development of the gut immune system. Gut-microbiota is also capable of synthesizing some vital metabolites inside the gut such as short-chain fatty acids, essential vitamins, and microbiome dysbiosis, however, might lead to disruption of the homeostasis of the immune system and mucosal barrier functions. This leads to subsequent inflammation resulting in increased mucosal barrier permeability and a continuous state of inflammation. Oral administration of distinct probiotic strain as a functional food has been suggested to affect multiple processes in host and reduces cancer risk. Probiotics are mono or mixed cultures of live organisms that confer beneficial health effects to the host upon ingestion in adequate amounts. The readily available probiotic preparations present in the market are mainly based on lactic acid bacteria. Probiotics show anticarcinogenic effects by reducing activities of microbial enzymes, inducing several cytokines which ameliorate or prevent tumorigenesis through modulation of the host's cellular immune responses, binding potential to

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carcinogen, producing antitumorigenic or antimutagenic compounds in the colon, altering physiologic conditions (such as pH) in the colon, affecting the metabolic activity of intestinal microflora. A wealth of indirect evidence based largely on laboratory studies has indicated the possible positive effects of probiotic consumption on cancer suppression.

Keywords

Probiotics · Gastrointestinal cancer · Anti-cancer · Homeostasis · Gut immune system

7.1 Introduction

An adequate number of viable organisms that stimulate other beneficial microorganisms' growth and aid in health after being administered to host are known as probiotic microorganisms. According to the latest definition, probiotics are defined as "live microorganisms which when administered in adequate amount induce health benefits in host" (Hill et al. 2014). Those bacteria which form the lactic acid bacteria (LAB) group include *Lactobacillus* spp., *Bifidobacterium*, *Streptococcus thermophilus, Enterococcus, Escherichia coli,* and *Saccharomyces boulardii*. Probiotics render anticarcinogenic effects via vivid modifications either in molecules or various metabolic and other pathways.

The human intestinal tract harbors over 400 different bacterial species. The gut microflora and its distribution are modulated by physiological interactions, diet, and other related factors. Many of the bacteria could not survive in the acidic pH of gastric juice and only acid resistant bacteria thrive in stomach. In addition, throughout the small intestine a transition region of low and high population of bacteria can be observed and colon region harbors large quantity of bacteria instead. Human gut–microbiota plays an important role in gastrointestinal homeostasis and modulates various functions of the same. Studies have also co-related gut-dysbiosis with various types of diseases including gastrointestinal (GI) cancers. GI cancer accounts for 25% among all kinds of cancer burden worldwide with increasing trend (Hill et al. 2014). GI cancer is malignant condition of gastrointestinal tract and organs related to it like esophagus, stomach, biliary system, pancreas, small intestine, large intestine, rectum, and anus. Surgery is the main means of treatment of GI cancer at present (Van Cutsem et al. 2016). Cardinal features of GI cancer include loss of certain functional events, inactivation of tumor suppressors and apoptotic pathways, epigenetic alterations (DNA methylation pattern), and aberrant gene expression and silencing (Lynch and Rustgi 2012). Majority of gastric cancer mainly occurs in developing countries and females are more commonly affected than males (Fig. 7.1).

Obesity and type 2 diabetes are mostly correlated with the occurrence of various kinds of GI cancers (Lynch and Rustgi 2012; Petruzzelli and Wagner 2019). Specific preventive strategies such as using functional foods containing probiotics could provide opportunities to mitigate obesity and metabolic health related

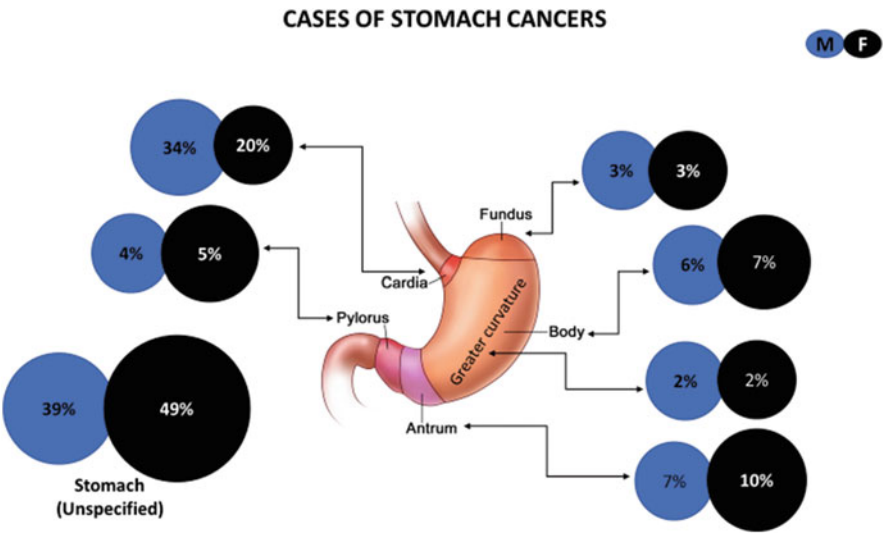

Fig. 7.1 Prevalence of stomach cancers in male and females

gastrointestinal cancers. The lack of early clinical signs of GI cancers leads to the development non-curable advanced disease state (Seidlitz et al. 2019) and as a result gastric cancer (Ferro et al. 2014) is now the fifth most common malignancy and the second leading cause of cancer-related deaths worldwide (Ferlay et al. 2010). According to The Cancer Genome Atlas (TCGA) Research Network, gastric adenocarcinoma can be divided into four different molecular subgroups (Fig. 7.1) (Ferro et al. 2014): those positive for the Epstein-Barr virus (EBV) with frequent *PIK3CA* mutations and *CDKN2A* silencing, a microsatellite instable (MSI) subtype with a hypermutation phenotype, a genomically stable (GS) subtype displaying diffuse histology and frequent *CDH1* and *RHOA* mutations and a chromosomal instable (CIN) subtype displaying aneuploidy and frequent mutation of *TP53* as well as activation of the receptor tyrosine kinase (RTK)-RAS pathway. Molecular characterization of AEG revealed their high similarity to the CIN subtype of gastric cancer (Ferlay et al. 2010) (Table 7.1).

In the last 20 years the incidence of gastric cancers dropped steadily but stomach cancer is still the second most prevalent cause for cancer related deaths worldwide (International Agency for Research on Cancer 1994). *Helicobacter pylori* (*H. pylori*) is considered as a class-I carcinogen and this represents a direct co-relation between infections with H. pylori and neoplastic transformations in the human stomach and one of the strongest known risk factors for gastric cancer (Correa 2013). *H. pylori* infections in humans induce both histological types gastric cancer (diffuse or intestinal types). Most important bacterial determinant that plays an important role in the development of gastric cancers are cytotoxin-associated gene pathogenicity island (*cag*PAI), vacuolating cytotoxin A (VacA), adhesion factors such as blood group antigen-binding adhesin (BabA) and sialic acid-binding adhesin (SabA)

Table 7.1 Data from cancer genome atlas

• Male prevalent • Located mainly in fundus and body • EBV-CIMP • Silenced CDKN2A • Amplified JAK2, CD274, PDCD1LG2 and ERBB2 • Enhanced immune cell signalling • Mutated Arid1a (55%) and BCOR (23%) mutated PIK3CA (80% subtype)	• Female prevalent • Gastric-CIMP • Silenced MLH1 • No such amplification • Mitotic pathway activation • Substitution mutations in TP53, KRAS, ARID1A, PIK3CA, ERBB3, PTEN AND insertion-deletion mutation in RNF43, B2M AND NF1 genes	• Diffusive in nature • Early age • Recurrent CDH1 (37%), mutated RHOA (15%) • Inactivated ARID1A • Integrin and syndecan mediated signalling are enhanced, increased angiogenesis	• Mainly found in gastro-esophageal junction/ cardia • Amplified RTK-RAS

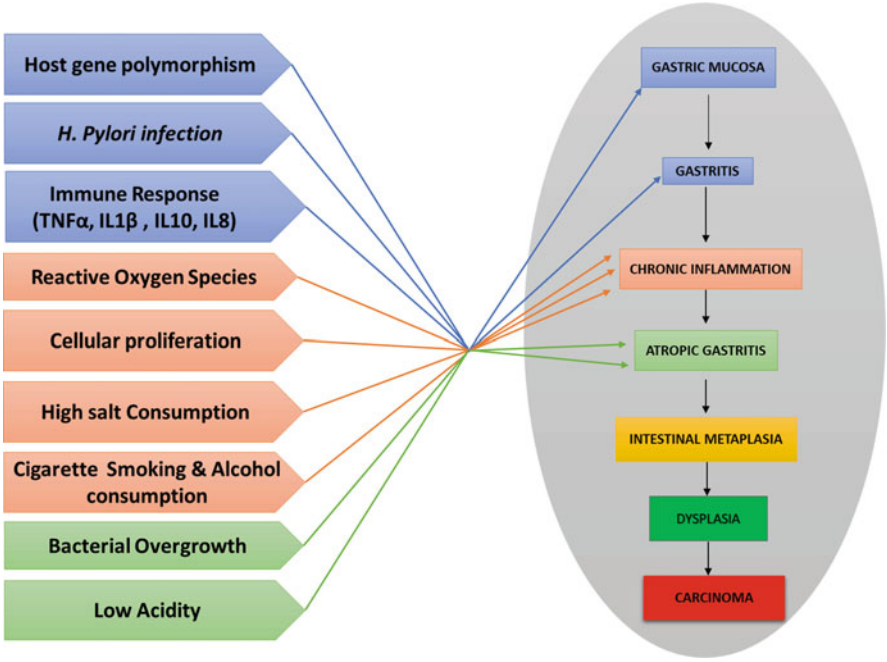

Fig. 7.2 Factors responsible for development of gastric cancer

(Boquet and Ricci 2012; Cover and Blanke 2005; Gerhard et al. 1999; Yamaoka et al. 2006; Sokolova et al. 2013) (Fig. 7.2). By activating one of the key regulators of inflammation such as nuclear factor kappa B (NF-κB), *H. pylori* activates cytokine signalling mediated by pro-inflammatory cytokines such as IL-8, TNF-α and STAT3, and drives the development of severe chronic inflammation and subsequently carcinogenesis and invasive carcinoma (Schweitzer et al. 2010; Aihara et al.

1997; Sharma et al. 1998; Beales et al. 1997; Suganuma et al. 2008; Ernst et al. 2008; Merchant 2008; Echizen et al. 2019). In addition, TNF-α promotes gastric tumor formation by activating a protein called NOXO1 (component of the NOX1 complex) which produces reactive oxygen species (ROS) and damages tissues. NOX1/ROS signalling induces gastric epithelial stem cells to multiply uncontrollably, resulting in tumor formation (Rhyu et al. 1994).

In addition, less than 10% of the cases of gastric cancer can be linked with inheritance. For example, familial inheritance of E-Cadherin is responsible for hereditary diffuse gastric cancers (HDGC). People with HDGC caused by CDH1 gene mutations are born with abnormally short, non-functional version of E-cadherin or alter the protein's structure. Specific genes such as MCC, APC, and p53 tumor suppressor genes are also involved in increasing the risk of gastric cancer (Trédaniel et al. 1997). Gastric adenocarcinoma, proximal polyposis of the stomach (GAPPS), and familial intestinal gastric cancer (FIGC) are other major syndromes accounting up to 3–5% of hereditary familial gastric cancers. There are also environmental and behavioral factors that could increase the risk of gastric cancers. Smoking, a high level of salt and processed meat in diet and high consumption of alcohol has been shown to increase the chances of gastric cancer development (Graham et al. 1990; Risch et al. 1985; Buiatti et al. 1989, 1990; van den Brandt et al. 2003).

As mentioned in the beginning of the chapter probiotic microorganisms show anti-cancer activities and they attribute these anti-cancer activities to mainly maintaining host-microbial balance of the intestine, reducing pathogenic and carcinogen producing microorganisms and their enzyme activities, clearing carcinogens by binding on them. Furthermore, several studies have shown the potential of probiotics in immune modulation, enhanced gut barrier function, anti-inflammatory effects, and reducing tumor formation and metastasis (Servin 2004; Cotter et al. 2005). Although more research is required for determining functional efficacy of probiotics on cancer prevention and treatment, probiotics can be still be considered as a potential nutraceutical and in this chapter, we will explore some of the established effects of probiotics on GI cancers.

7.2 Types of GI Cancer, Associated Risk Factors, Diagnosis and Treatment

7.2.1 Pancreatic Cancer

Pancreas is a glandular organ of body comprised of endocrine and exocrine components. The endocrine system secretes out insulin, glucagon, and somatostatin while exocrine part secretes different enzymes for digestion of food. Pancreatic cancer shows three phases: acute, chronic, and metastasis (aggressive, chemo-resistant) pancreatitis (Singhal et al. 2016).

7.2.2 Liver Cancer

The function of a liver in body is to aid in digestion process. A healthy liver could start to develop liver damage or uncontrolled cell growth that could lead to two stages of liver cancer (a) benign tumor and (b) hepatocellular carcinoma (HCC)—malignant stage. HCC is frequent in patients with liver cirrhosis. The major risk factors for the development HCC are chronic viral infections mediated by either hepatitis B or hepatitis C or excessive alcohol consumption (Aham et al. 2013; Batey et al. 1992; Morgan et al. 2004). The diagnosis of liver cancer starts with the identification of liver cirrhosis in patients that gives a possibility of presence of tumor. An ultrasound test is done to identify the nodule as well as blood test is done to screen out a protein called α-fetoprotein. If the higher level of this protein is present in blood, it gives a clue of liver cancer (Johnson 2001). The symptoms encircle weight loss, fatigue, nausea/vomiting, fever, swelling of abdomen, jaundice, enlarged liver, etc. The diagnosis includes blood tests, radiological and histopathological examination.

7.2.3 Stomach Cancer

The tissue lining (mucosa) of the stomach is prone to cancer because it remains the site of initiation of cancerous tumor cells. Various types of stomach cancers such as gastric lymphomas originate from cells of immune system present in stomach wall. They are usually non-Hodgkin lymphomas. Gastrointestinal stomach tumors (GIST) are rarely occurring tumors which originate from the tissue of inner lining of stomach and intestine. Neuroendocrine tumors are believed to originate from nervous or endocrine cells of stomach. Environmental factors, nutritional factors and *H. pylori* infection have been implicated in the development of the stomach cancer (Sasazuki et al. 2006). Diagnosis of stomach cancer is not very predictable as symptoms are subtle and simple like abdominal pain, indigestion, vomiting, weight loss, blood in stool, poor appetite, or swelling of abdomen. Clinical examination including detection of tumor markers such as carcinoembryonic antigen (CEA), the carbohydrate antigens (CA)—CA19–9, CA-72-4, CA125, CA24–2 and alpha fetoprotein, endoscopy, endoscopic ultrasound, radiological examination as well as histopathological examination remains the choice of diagnosis of stomach cancer (Tong et al. 2016; Kotzev et al. 2018). The treatment plan includes surgery with removal of stomach or total gastrectomy, removal of lymph nodes or/and removal of other related organs (Otaka et al. 2006). Adjuvant therapy (a combination of chemo and radiotherapy) is given in addition to surgery (Ushijima et al. 2004; Earle et al. 2002).

7.2.4 Colorectal Cancer

Unregulated growth of cells in colon or rectum is called colorectal cancer (CRC). The colon and rectum together (colorectum) constitute the large intestine and the final parts of the GI tract. CRC is sometimes referred to as bowel cancer. The former part of large intestine is colon which is divided into four sections: (1) ascending colon: starts from cecum and extends to right side of the abdomen. (2) transverse colon crosses the body from right to left side and is known as proximal colon (3) descending colon extends to left side (4) sigmoid colon named after its shape, i.e. "S" which is the final portion of the colon and then joins rectum.

Early CRC often has no symptoms and as the tumor grows, it may obstruct the intestine resulting in blood loss. Bleeding from the rectum, blood in the stool, dark or black stools, change in bowel habits, weakness, excessive fatigue are the additional warning signs. CRC starts with noncancerous cellular growth termed as polyp which grows attached to the inner lining of the colon or rectum. The most prevalent type is adenomatous polyp or adenoma (Amersi et al. 2005) which arises from glandular cells whose function is to lubricate the colorectum. Although all adenomas have potential to grow as cancerous cell but only 10% are invasive cancerous cells. This type of tumorous growth is termed as adenocarcinoma. These can proliferate and invade through blood vessels or lymph vessels and via this means they spread fast.

7.2.4.1 CRC Stages Using the Surveillance, Epidemiology, and End Results (SEER) Summary Staging System

In Situ In this stage cancers have not yet begun to invade the wall of the colon or rectum.

Local Cancers that have grown into the wall of the colon or rectum, but have not extended through the wall to invade nearby tissues.

Regional Cancers that have spread through the wall of the colon or rectum and have invaded nearby tissue, or that have spread to nearby lymph nodes.

Distant Cancers that have spread to other parts of the body, such as the liver or lung.

The risks (Amersi et al. 2005) associated with the development of colorectal cancer are enlisted here.

Age Age is one of the prime factors that shows an increasing age has higher risk of acquiring CRC but affects men and women in different age groups. Men tends to acquire the disease at the age of 68 whilst women in 72 and later. The median age of CRC diagnosis is about 40–50 years (Kemppainen et al. 1993; MacGillivray et al. 1991).

Gender CRC is more prevalent in men than in women where they are reported with 30% higher risk of the disease. There could be unidentified reasons for the gender disparity in disease occurrence (Wei et al. 2004).

Ethnicity or Race Worldwide non-Hispanic blacks are more prone to the disease while this occurrence was lowest in Asians and Pacific islanders. Alaska natives specifically rural natives are at higher risk of infection by *H. pylori* and hence associated risk of cancer in colon or stomach (Parker et al. 1998; Freeman et al. 2002).

Family History of Colorectal Cancer There is a risk of 30% a person acquires the disease from the family line with the case history of CRC. The risk is higher for the people with many first-degree relatives suffering from the same (Lynch et al. 2003).

Personal Medical History: Chronic Inflammatory Bowel Disease When colon remained inflamed over a long period of time it results in chronic inflammatory bowel disease. Most common forms of the diseases are ulcerative colitis and Crohn's disease. There are increased chances of developing the cancer if the inflammation persists (Bernstein et al. 2001; Gyde et al. 1988).

Personal Medical History—Diabetes The persons with type 2 diabetes are at higher risk of attaining the CRC. Dysregulation of insulin signalling and glucose control, leading to hyperinsulinemia and inflammation, are important biological pathways for the development of this cancer (Peeters et al. 2015; Mills et al. 2013).

Obesity Obese people are at prior risk of getting CRC. Lower body and metabolic activities may lead to the deposition of fats. Although obesity is associated with an increased risk of colorectal cancer, individuals with obesity without raised insulin levels do not have elevated risk of CRC (Bardouet al. 2013; Ma et al. 2013). However, lean individuals with hyperinsulinemia had an increased risk of colorectal cancer of a similar magnitude to individuals with obesity and hyperinsulinemia.

Diet Few dietary elements are directly linked to regulate CRC like calcium intake and dairy products decline the risk of adenomas and CRC, fibers prevent colon cancer, folate intake with diet promptly inhibits the risk of new tumor formation, fruits and vegetables contain dietary fibers and nutrient that decreases the risk of tumor formation (Terry et al. 2001; Baron et al. 1999). But intake of red and processed meat influence to greater risk of colorectal cancer which is related to some ingredients in the meat. Vitamin D could downregulate the occurrence of CRC (Kampman et al. 1999; Fuchs et al. 1999).

Consumption of Alcoholic Beverage and Smoking Heavy usage of alcohol and smoking leads to development of CRC (Verma 2009; Cho et al. 2004).

7.3 Role of *H. pylori* in Gastrointestinal Cancer

It is said that *H. pylori* originate in Africa and over 50% population worldwide is affected from *H. pylori* but it is more prevalent in developing countries. The bacterium can be acquired right from the childhood showing symptoms of gastroenteritis. The *H. pylori* infection also leads to deficiency of vitamins like A, B12, C, E and micronutrients such as copper and iron. A lot of studies have revealed how *H. pylori* is infectious to human stomach and digestive tract. Among various mechanisms one is alteration of antioxidant properties of melatonin because they scavenge the available antioxidants in the host body but they are reduced in number if higher concentration of ascorbic acid is available in the host. Ultimately, the bacterium is able to change the redox potential of these antioxidants and leading to oxidative stress in the digestive system. Several diseases could develop along with the *H. pylori* infection in the human, viz. (1) higher chances to acquire cholera disease, (2) development of acne and induce infection by Acne vulgaris (etiological agent of acne), (3) HP infection onset the hyperprolactinemia which later induces Polycystic Ovarian Syndrome (PCOS), (4) rise in blood pressure level, (5) escalated risk of ischemic heart disorder, (6) higher risk of attaining diabetes, (7) post treatment weight gain. *H. pylori* is a potential carcinogen (defined by WHO) due to certain reasons, viz. (1) it leads to the development of adenocarcinoma, and (2) MALT (mucosa associated lymphoid tissue) lymphoma (Alfarouk et al. 2019). In addition, the development of gastric cancer is also dependent on health and immune status of the host as well as the nature of the *H. pylori*.

The onset of *H. pylori* mediated carcinogenesis includes several genes and related factors in the microenvironment. Following is the listed factors that are involved in the GI carcinogenesis related to *H. pylori*:

Ureases enzyme (cytoplasmic enzyme) creates a suitable microenvironment for the *H. pylori* bacteria to grow and establish in the acidic environment of stomach because the enzyme catalyzes the substrate urea and releases ammonia and carbon dioxide which neutralizes the acidity and buffers the acid neutralized environment that becomes suitable for the growth of bacteria. Facilitated diffusion is mediated by urease enzyme in the mucus membrane. Ureases also alter the host immune response towards *H. pylori* but not the pathogenesis of the bacteria. A transporter has been identified encoded by the *ureI* gene capable of delivering urea to the cytoplasm where urease enables neutralization and buffering capacities. Hence, it is invincible that urease enzyme is an important factor that facilitates the establishment of *H. pylori* (Weeks et al. 2000). Acidic pH prevails bacterial enzyme synthesis such as arginase and carbonic anhydrase (MacGee et al. 1999, 2008).

Arginase is involved in providing the substrate to urease to produce L-ornithine and urea.

Carbonic anhydrase (zinc containing metalloenzyme) catalyzes the interchangeable reaction of carbon dioxide and water to form carbonic acid; this gets dissociated to form bicarbonate liberating hydrogen ion (H^+). The enzyme is omnipresent in both prokaryotes and eukaryotes in cytoplasm and organelle like mitochondria and cytoplasmic membranes. The CA enzyme is functionally related to buffering and

biosynthetic processes in cells. Two different forms of CA exist in *H. pylori* (a) α-type CA (HpaCA) and (b) HP β-CA (HpbCA). HpaCA encourages urease activity and HpbCA is associated with growth of bacteria in acidic environment.

H. pylori expressed Lewis antigen is a constituent of lipopolysaccharide of bacterial (*H. pylori*) cell wall. The Lewis antigen is a part of human blood group that is encoded by the genes present in chromosome 19 p13.3 (FUT3 or Lewis gene). *H. pylori* expressed Lewis antigen mimics the human type Lewis antigen because the O-antigen (side chain of LPS) shows homologous structure with that of the human Lewis antigen. The mimicry allows the *H. pylori* to overcome the immune defense system of the human beings. This also facilitates the adherence of *H. pylori* to the gastric epithelial mucosal cells. But humans that have blood group A and B are likely to resistant to infection by the *H. pylori*. The expression of Lewis antigen in different *H. pylori* strains is different with genes such as Lex, Ley, both, Lea, Sialyl-Lex or negative for both. Lex and Ley are correlated with cagA+ and s1/m1 VacA. Among the western population, the dominant phenotypes are LeX and Ley while Lea and Leb are found in a smaller proportion. Possessing of Lex and Ley leads to higher *H. pylori* internalization rates by gastric epithelium as compared to Lea and Leb or non-expressing Lewis antigen.

VacA is a vacuolating cytotoxin encoded by vacA gene that is secreted out. All strains of *H. pylori* contain vacA gene but all may show variable expression. Secretion of VacA is prominent in patients suffering from GI cancer. The toxin is made of two subunits say, P55 and P33 proteins. The former is responsible for creating pores in the epithelial layer while the latter one disintegrates mitochondrial fission system. These lead to cellular death of the epithelial tissue. Maturation and sorting of lysosomal enzymes are adversely affected by the VacA which also inhibits T-cells population.

Cag A (Type IV protein secretion system (*T4SS*) encoded by cagA gene) delivers cagA-oncoproteins which decline apoptosis. The usual target of cagA is mitochondria that lead to respiratory impairment of cancer cells. The HP induced pathogenesis is heterogenous in the way that if cagA+ is in association with the gastric adenocarcinoma development then either cagA+ or cagA- could induce B-lymphoma which triggers IL2 expression via T cells. cagA is also related to higher cytokines production rate. The cagA+ gene product alters epithelial activity because it now acts as phosphatase enzyme for catalyzing dephosphorylation reaction that induces a pro inflammation with release of IL-8, MAPK, and NF-BK which are signature of carcinogenicity.

Exterior proteins (*BabA2*) is a membrane exterior protein whose presence is an indication of GI cancer and is encoded by babA2 gene. It shows binding with Lewisb (Le b). The presence of combined proteins, i.e. BabA2, CagA, and Vac A indicates the probability of carcinogenesis.

7.4 Key Elements of Humans in Response to *H. pylori* Induced Gastric Cancer

Human body shows response to inflammation caused by *H. pylori* in several modes showing a variety of elements that are produced at the onset of the cancer. Few are enlisted:

β-catenin: It is a CTNNB1 gene encoded protein present on band p12 at short arm of chromosome 3. This is the region which gets affected by somatic alterations in tumors. This protein coordinates for cell–cell adhesion as well as gene transcription. β-catenin is a proto-oncogene that has been found to accumulate inside the nucleus in precancerous lesions of gastric cancer. β-catenin is related to vivid kinds of tumors, viz. hepatocellular carcinoma, ovarian carcinoma, breast cancer, lung cancer, colorectal cancer, basal cell carcinoma, prostate cancer, pilomatrixoma, medulloblastoma, head and neck squamous cell carcinoma, and glioblastoma.

Epidermal growth factor receptors (*EGFR*) are proteins in relation to tyrosine kinase receptor like Her 1, Her 2, Her 3, and Her 4. These are cell surface receptor proteins that are expressed in many of the carcinomas.

Immunological response towards H. pylori: mutagenic substances are formed in response to tumorigenic inflammation by *H. pylori* such as nitric oxide synthase enzyme (iNOS) which releases free reactive nitrogen species that diminish antioxidative agents.

Enzyme phospholipase A_2 (PLA_2): this enzyme catalyzes the reaction involving fatty acids releasing off arachidonic acids that later convert into prostaglandins and leukotriene with the help of enzymes cyclooxygenases and lipoxygenases. Prostanoids are produced from prostaglandins by the action of cyclooxygenase 1 and 2. The role of prostanoid is to increase the production of pro-aggregatory prostanoid, thromboxane via platelets which all induce TNF-α, TNF-γ and IL-1 that are related with colorectal cancer. Leukotriene is related to gastritis whose receptors are expressed in gastric cancer cells.

7.5 How Probiotics Interrupt Gastrointestinal Cancers

Probiotics have been used to manage a number of GI disorders such as diarrhea, infection, and inflammation. There are several ways that probiotics defend our body from cancer (Fig. 7.3). Among all the mechanisms available in literature one is replacement of gastrointestinal microflora, deactivation of carcinogens, competitive interaction with pathogenic microorganisms, enhancement of immunity, antiproliferative action on carcinogens such as apoptosis and tissue differentiation, aids food digestion, inactivation of tyrosine kinase signal pathways (Li et al. 2014; Chen et al. 2012; Del Giudice et al. 2009; Yang et al. 2012; Hsieh et al. 2012). These and other mechanisms by which probiotics could inhibit the chances and/or onset and progression of GI cancers are given in Table 7.2.

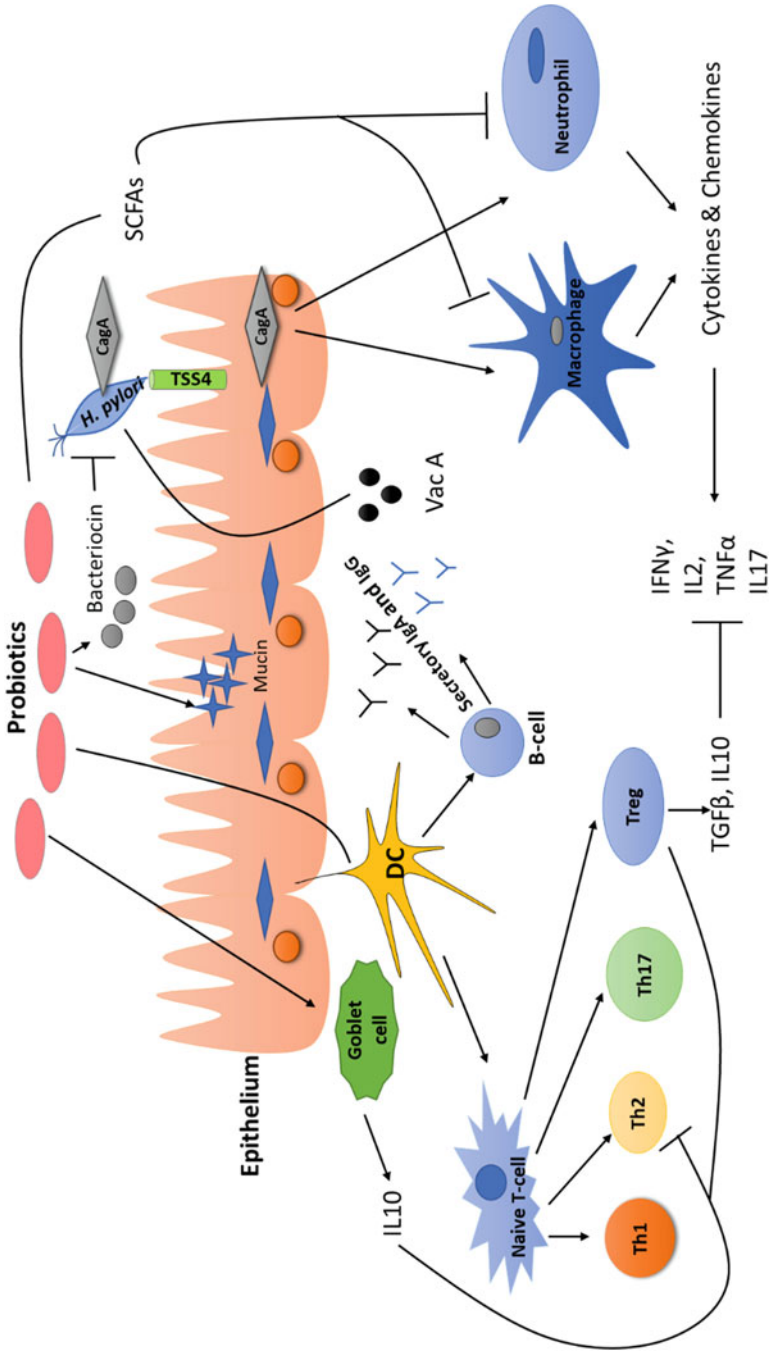

Fig. 7.3 Possible mechanism of actions of probiotic bacteria in the immunomodulation and the anti-inflammatory response in the gut. Macrophages, dendritic cells and other immune cells may involve in preventing pathogens, gastric inflammation and cancer

Table 7.2 Combating risk factors of GI cancer with aid of probiotics

Risk factors prone to GI cancer	What probiotics play	References
Gut microbiota (increase in opportunistic pathogens) *bacteroides, fusobacterium, salmonella, prevotella*	Replacement with LAB group, *Bifidobacterium, Lactobacillus* which even declines the population of *Escherichia* and *Staphylococcus*	Marteau et al. (2001)
Disturbed physio-chemical conditions in GI organs viz. incomplete fermentation or digestion, alkalosis, water absorption rate, toxic fecal water content	Probiotics facilitates fermentation and decreases pH while simultaneously decreases products like putrescine, cadaverine and tryptamine (substances shows putrefaction)	Lebeer et al. (2008)
Epithelial line damage (show higher permeability along with pathogen translocation, rearrangement of proteins at tight junction)	Recovery of damage in epithelial barrier by specialized proteins like defensins, heat shock proteins (cryoprotective) along with mucus production that leads to normal survival of epithelial cells	McBain et al. (2001)
Increased production of bacterial enzymes that harm the gut (β-glucoronidase, β-glucosidase, azo-reductase, nitro-reductase, alcohol dehydrogenase)	Population of bacteria producing the harmful enzymes is reduced (*Clostridium, Bacteroides, Salmonella, Citrobacter, Escherichia, Enterobacter, Enterococcus, Escherichia, Staphylococcus, Streptococcus*)	Weisburger (1971)
Production of carcinogenic metabolites (iq, tryptophanase, urease, acetaldehyde, mnng, n-nitroso compounds, sodium azide, aromatic amines, aflb1, trp-1, transformed bile salts, indoles, aglycones hydrogen sulfide, benzo–α-pyrene)	Destabilization of carcinogens: production of antioxidants and enzymes that detoxify the carcinogenic metabolites either by binding to it or deactivating them (GTS, catalase, glutathione, glutathione reductase, superoxide dismutase, glutathione peroxidase)	Waldecker et al. (2008)
Dna damage activity is increased (absurd cell growth, tumor development, dysplasia)	Production of anticancerous metabolites by probiotics (phenols, CLAs, SCFAs) shows increased apoptosis and differentiation in cancer cells	Azad et al. (2018)
Development of inflammation in intestine (higher production of nf-κb, il-8 and il6), this leads to decreased immune response towards tumor cells	Lowers intestinal inflammation by lowering TLR-4 and activating immune response against those tumor cells, activation of regulatory T cell, increased bactericidal phagocytosis stimulation of DCs and natural killer cells	Zhong et al. (2014)

7.5.1 Mechanisms of Probiotics Altering the Onset of GI Cancer

The metabolic process in the stomach and small intestine get shifted with the changes of micoflora present thereby the replaced microflora also replaces the metabolites, pathways and enzymes in the system. In liver, metabolism of

glucuronide conjugation occurs where conjugation of glucuronic acid takes place resulting in liberation of polar metabolites. The process of deconjugation of these polar metabolites takes place in intestine through bacterial enzymes (β-glucuronidase) releasing aglycones which is a potent carcinogen. Few other examples of these enzymes are azo-reductase and nitro-reductase which also release toxic carcinogenic metabolites in the intestine (Marteau et al. 2001). The consumption of probiotics or synbiotics reduces the potential risk of cancer development by replacing these enzymes which ultimately results in different metabolic pathway. Probiotic food like yogurt contains *lactobacilli* that replace the fecal enzyme if taken simultaneously for few days (Uccello et al. 2012). In a research conducted by Marteau et al. (2001) a decline in nitro-reductase activity was observed after taking dairy products including *L. acidophilus*, *B. bifidum,* and mesophilic cultures (*Streptococcus lactis* and *Streptococcus cremoris*) but the two enzyme β-glucuronidase and azo-reductase did not alter.

7.5.1.1 Carcinogens Replacement by the Probiotics

Consumption of red meat is one of the risk factors associated with CRC because when it is cooked at much elevated temperature heterocyclic aromatic amines (HCA) are produced which later involves the intestinal microbiota to further liberate mutagenic metabolites such as 3-amino-1,4-dimethyl- 5H-pyrido-[4,3-b] indole [Trp-P-1], 3-amino-1-methyl-5Hpyrido-[4,3-b]indole [Trp-P-2], 2-amino-3-methylimidazo [4,5-f] quinoline [IQ], 2-amino-1-methyl-6-phenylimidazo [4,5-b] pyridine [PhIP], 2-amino-3,4-dimethylimidazo[4,5-f] quinoline [MeIQ], and 2-amino-3,8-dimethylimidazo[4,5- f]quinoxaline [MeIQx] (Rhee et al. 2001). The release of such mutagenic compounds interacts with mucosa of colon and leads to tumor formation. When probiotic microorganisms are present in the intestine, they bind to these mutagenic compounds and modify them so these could not have an impact on the colonic mucosa. In a study, the genotoxicity was downregulated by oral administration of probiotic strains of *L. acidophilus* and *B.* spp. which was found to bind with the mutagen Trp-P-1 irreversibly (Rafter et al. 2007).

7.5.1.2 Competitiveness with the Pathogenic Microflora

The colon region of the GI tract is the most burdened with bacteria. These bacteria are usually normal flora but could be an opportunistic pathogen which could lead to initiation of acute or chronic disorders. The diet of a person reflects the type of microflora harboring in the gut; as already mentioned, red meat intake leads to production of carcinogens but also alters microbiota which increases the population of sulfate reducing bacteria that produces hydrogen sulfide (genotoxic compound). Some putrefactive bacteria also reside in the colon that creates an environment for onset of CRC namely, *Clostridium* and *Bacteroides* spp. A researcher found a decline in the fecal flora of polyp and colon cancer patients after they were administered with certain group of LAB (*Bifidobacterium*, *Lactobacillus* sp.), simultaneously there was a decline in the number of Clostridium sp. (Gianotti et al. 2010).

7.5.1.3 Probiotics to Improve Host Immune System

The suppression of tumor and its progression is largely undertaken by host immune system. An array of immune system components plays their role such as antigen presenting cell (APCs), natural killer cells, T and B cells but apart from these probiotics are believed to improve the immunity of a person and is also evident from several research done in this regard. A strain designated as *L. casei* Shirota (LcS) was observed among other potential LAB that suppressed transplantable mouse sarcoma (Yokokura et al. 1981). This strain does not directly suppress tumor but enhance the immunity of the host by increasing the number of cytokines, viz. Interferon- γ (INF-γ), Interleukin –β (IL-β), and tumor necrosis factor-α (TNF-α), thus tumor is suppressed (Fig. 7.3). The suggested mechanism behind the immunity improvement is when probiotics are ingested by a person it binds to M cells in Peyer's patches, macrophage or dendritic cells (DCs). Then the phagocytic process is triggered to digest these LcS several cytokines are generated. Thereafter, the LcS digested components are recognized in Peyer's patches by toll like receptor-2 in APCs wherein again several cytokines are generated. Side by side natural killer cells do play a vital role in activating immunity. Natural killer cells are granular lymphocytes which are bone marrow derived cells and are activated by probiotics. In a double-blind study, a mixture of two probiotic species *B. longum* (*BB536*) and *L. johnsonii* (*La1*) was administered to the patients and it was found that *La1* reduces the concentration of gut pathogens and modulates the local immunity by adhering to the colonic mucosa (Culligan et al. 2009).

7.5.1.4 Effects on Apoptosis and Tissue Differentiation

Apoptosis is defined as a genetically programmed process of regulating cell numbers that control vital role in preventing cancer. In many cancer cases, apoptosis does not initiate in response to uncontrolled cell growth. In this regard, probiotics provide a great help in controlling proliferative growth of cancer cells or initiating apoptosis.

7.5.2 Variety of Probiotic Microorganisms Showcase Anticancerous Action Towards GI or Colon Cancer

Antitumor activity is studied on animals using a variety of probiotic bacteria; *B. longum* to show inhibition of liver cancer in mice, simultaneously *B. infantis* and *B. adolescentis* when injected subcutaneously and intravenously into those mice had shown antitumor action (Wei et al. 2018). In a randomized controlled trial, the effective role of probiotics against acute gastroenteritis was done in selected group of infants and adults to judge the declination in HP via probiotics using array of probiotic bacteria, namely, *L. rhamnosus* strain GG, *Enterococcus faecium* SF68, *Saccharomyces boulardii, L. reuteri*, and yogurt (a traditional probiotic food) (Marteau et al. 2001). Probiotic microorganisms such as *L. acidophilus, L. gasseri, L. confuses, Streptococcus thermophiles, B. breve* and *B. longum* reduce genotoxicity in GI cancers after administered orally mainly via inhibitory actions against N′-nitro-N-nitrosoguanidine (MNNG) and 1,2-dimethylhydrazine (Consoli

et al. 2016). Probiotics are capable of modulating the gut microbiome along with systemic and immune response of the consumer (Table 7.3). Probiotics not only have the capability of preventing and inhibiting the carcinogenic agents but they are equally effective in preventing complications of cancer treatments. Probiotics induce these effects partly by producing soluble compounds that may interact directly with tumor cells in culture and inhibit their growth (Wan et al. 2014).

7.5.2.1 Probiotics in Colon Cancer

The colon region of GI tract harbors a vast number of bacteria whose composition may affect the chances of cancer. The replacement of these microflora by probiotics prevents the onset of carcinogenic activities. Induction of cell apoptosis by *L. rhamnosus* in animal model with colon cancer is reported. Inside colon the fermentation of prebiotics releases short chain fatty acids (SCFA) like butyrate which is significant in ulcerative colitis. In addition to this, sodium butyrate is a strong inhibitor of growth and inducer of phenotype differentiation and apoptosis while reduces risk factors involving colon cancer and adenoma. In a clinical trial conducted in 2016 further demonstrated that randomized oral administration of the probiotic *Saccharomyces boulardii* in CRC patients downregulates pro-inflammatory cytokines (Yu et al. 2016).

7.5.2.2 Breast Cancer

It has been reported that the routine consumption of probiotic *Lactobacillus casei* enhances the immune response of breast cancer patients. Nanotechnological interventions with probiotics (*L. plantarum*; yogurt) have shown improved production rate of cytokines IFN-γ, TNF-α and IL-2 and NK cells (Mendoza 2019).

7.5.2.3 Bladder Cancer

It has been shown in a research that intake of probiotics is efficient against bladder cancer. Transurethral Resection of Bladder Tumor (TURBT) is a procedure in which bladder tumors can be removed but recurrence of the tumors can be observed regularly. After TURBT, as compared to the intravesical epirubicin alone, oral administration of *L. casei* with combination of intravesical epirubicin reduces recurrence rate of bladder tumors more significantly (Sharifi et al. 2017; Shah 2007; Naito et al. 2008; Aso et al. 1992; Panebianco et al. 2018).

7.5.2.4 Other Cancers

Recently, few other studies have suggested the beneficial effects of probiotics on other GI cancers. Probiotics could prevent pancreatic cancer by modulating pancreatitis, diabetes, pancreatic necrosis, inflammation, and obesity (Rafter 2003; Gamallat et al. 2016; Olah et al. 2002, 2007; Liong 2008; Kim et al. 2008). In vivo studies with mice have been reported that probiotic administration could inhibit progression of hepatocellular carcinoma (HCC). Even liver-tumor size has been reduced when tumor injected mice were supplemented with probiotic mixture.

Table 7.3 Probiotics to encounter cancer and other related infections

Role played	Probiotics	Mechanism	Reference
Antioxidant activity	*B. longum, L. acidophilus*	Inactivate ROS via enzymatic mechanism (coupled NADH oxidase, peroxidase and catalase)	Azad et al. (2018)
Immune response improvement	LAB: *L. acidophilus*	Release of cytokines, IL-10, down regulation of IL-2 and TN-α, activation of CD4+ T cells.	Azad et al. (2018)
Short chain fatty acid production	*Buty vibrio fibrisolvens* MDT-1, *Propionibacterium acidipropinici* (propionate and acetate producer)	Produces high amount of butyrate which reduces aberrant crypt foci (ACF) in mouse model of colon cancer, reduces glucuronidase activity	Zhong et al. (2014), Wei et al. (2018)
Anticarcinogenic, antimutagenic and antioxidative effect	Kefir: fermented kefir grains with *L. paracasei, L. kefiri, L. parabuchneri, Acetobacter lovaniensis*; yeast: *Saccharomyces cerevisiae* and *Kluvveromyces lactis*	Bacteria convert lactose to lactic acid thus decreasing the milk pH, yeasts produce ethanol and CO_2, kefir is also rich source of vitamins (A, B1, B2, B5, C, B12 and folic acid) and amino acids (serine, lysine, alanine, threonine, tryptophan, valine, lysine, methionine, phenylalanine and isoleucine). Bioactive peptides in kefir induce activation of macrophages and phagocytosis and nitric oxide production along with production of TNF-α and cytokines (IL-5, IL-6, IL-1α, IL12)	Consoli et al. (2016)
HP infection suppression, antidiarrheal, anticarcinogenic, improves lactose metabolism	Traditional yogurt: a probiotic dairy product made out of fermentation of milk using starter cultures of *L. acidophilus*, *Bifidobacterium* sp., *L. casei*; now other bacteria used are *L. casei* Shirota, *L. rhamnosus* GG, *L. reuteri* along with the aforesaid	Lactic acid produced by these bacteria shows antimicrobial activity, reduced colonization of HP, decreases the level of certain enzymes such as β-glucuronidase, azo-reductase and nitro-reductase. Produces IF –α and NK cells	Wan et al. (2014)
RS retards tumor growth in pancreatic cancer	Prebiotics: resistant starch	Resistant starch promotes the growth of bacteria involved in butyrate production	Yu et al. (2016)

7.6 Conclusion

Recent studies have supported the idea that probiotic consumption may involve in immunomodulation, reduction of tumor development and establishment of healthy gut in gastric cancer patients. Probiotic microorganisms in formulation have the anti-toxic and anticarcinogenic potential that eliminates toxics and tumorigenic substances produced after digestion in the gut. Probiotics bacteria have the ability to modulate the immune system by alteration of the cytokines production and signalling pathways related to epithelial cell inflammation and tumor initiation. Although there is still lack of direct evidence of how probiotics induces its actions, however research in this field still has to progress towards a concrete understanding of molecular mechanism of the microorganisms with human hosts. Current therapies that are available for different types of GI cancers includes chemotherapy, radiotherapy immunotherapy and targeted therapy comes with diverse side effects in patients.

Now we are looking for safe natural products as an alternative to the conventional drug-based therapy for routine health care and disease management. Probiotics have recently emerged as safe, cost-effective and easily affordable as prophylactics for management of gut related inflammatory disorders. Therefore, probiotics would be used as biotherapeutic agent for the treatment of cancer and other inflammatory diseases which can maintain a homeostatic balance between inflammation and tumor progression.

Furthermore, the use of modern biotechnology approaches to construct designer probiotics to achieve targeted health benefits is vital in the present era. The designer probiotics may have promising results against gastric inflammations and other related disorder due to their unique ability to modulate and regulate the host's immune response by initiating the activation of specific genes in and outside the host intestinal tract. The aim of this book chapter is to emphasize the promising beneficial impact of probiotics on human health for better lifestyle.

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