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Review Article

IMBALANCE OF GUT MICROBIOTA INDUCES CANCER: A REVIEW

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Abstract: Human intestine harbors both pathogenic and non-pathogenic micro- organisms, the later generally have symbiotic relations with the host. In a healthy person a ratio between them most of the time remains constant; however, the ratio is disturbed due to many reasons, including change in dietary conditions. The chronic imbalance between the two groups may turn out to be a serious health problem for the host. Many studies have indicated that gut microbiota is responsible for the health and integrity of the colon but if the beneficial bacterial population is decreased then not only, conditions for development for cancer and many other inflammatory and autoimmune diseases intensifies.

Key words: Gut microbiota, Cancer

INTRODUCTION

Humans are living in the ocean of microorganisms, they are found in the air we breathe, the water we drink, bathe, swim and sail our boats, and the earth on which we are dependent from birth to death and even after the death. These microbes invade even the deepest part of our body; not only skin, they are also found in gastrointestinal tracts, mammary glands, placenta, seminal fluid, uterus, ovarian follicles, lung, saliva, oral mucosa and conjunctiva. These microbes belong to the groups of bacteria, archaea, protists and viruses. It was believed that bacteria and other recalculated and was found that the ratio between resident microbes and human cells is more likely to be one-to-one. A 'reference man' (one who is 70 kilograms, 20–30 years old and 1.7 meter tall) contains on average about 30 trillion human cells and 39 trillion organisms [1]. We are dependent on these bacteria to help digest our food, produce certain vitamins, regulate our immune system and keep us/ healthy/ by protecting us against disease-causing bacteria.

The term "microbiota" is coined for an "ecological community of commensal, symbiotic and pathogenic microorganisms" found in and/or on all multicellular organisms studied to date from plants to animals. The human microbiota is aggregate of microorganisms that reside on or within any number of human tissues and bio-fluids. The human microbiome specifically refers to the collective genomes of resident microorganisms [2]. Some microbiota that colonizes human are commensal, others have a mutuality relationship with their hosts. Conversely, some non-pathogenic microbiota can harm hosts via the metabolites they produce, such as trimethylamine [3,4] which is exclusively a microbiota - derived product of nutrients from normal diet. Rapid advances in microbiology and genetic research techniques have uncovered a significance previously underestimated microbial contribution and its

metabolic and developmental impact of microbiota.

Certain microbiota performs tasks that are known to be useful to the human host; the role of most resident microorganisms is not well understood. Those that are expected to be present and that under normal circumstances do not cause disease are sometimes deemed normal microbiota [3].

When we are first born, our bodies are quite pristine and the digestive tract is sterile. Immediately we are presented with breast milk and exposed to environmental factors, both of which begin colonizing our digestive tract with bacteria - most of them beneficial and harmless. As we grow older and are introduced to new substances and bacteria species, more species colonize the gut. They are the beginning of our natural defense system. This co-dependent, symbiotic relationships formed in the fetal and neonatal stages extend into adulthood and even across the generations [5].

The gut microbiota became essential for the maintenance of the health and integrity of the colon. There are more bacteria in the gastrointestinal tract than there are cells in the body. The bacteria in our gut weigh approximately 2 kg. There are about 400-1000 different species of bacteria in our GI system. Infect gut microbiota considered as "forgotten organ" due to the extensive role they play. Recently accumulated evidence suggests that imbalance in population of gut microbes may result in colorectal cancer. In this review we are unfolding the phenomenon of imbalance of microbiota in the induction of cancer and mechanisms therein.

Human microbiome project: In 2012, Francis Collins has created a reference database and the boundaries of normal microbial variation in humans by mapping the normal microbial make-up of healthy humans using genome sequencing techniques [6]. All DNA, human and microbial, obtained from several volunteers were analyzed with DNA sequencing machines. The microbial genome data were extracted by identifying the bacterial specific ribosomal RNA (16S rRNA). The researchers calculated that more than 10,000 microbial species occupy the human ecosystem and they have identified 81- 99% of the genera.

Gut microbiota: The gut microbiota has the largest numbers of bacteria and the greatest number of species compared to other areas of the body [3]. In humans the gut microbiota is established at one to two years after birth and by that time the intestinal epithelium and the intestinal mucosal barrier that it secretes have co-developed in a way that is tolerant to and even supportive of the gut microbiota and that also provides a barrier to pathogenic organisms [7].

The relationship between some gut microbiota and humans is not merely commensal, but rather a mutualistic relationship [1]. Some human gut microorganisms benefit the host by fermenting dietary fibers into short-chain fatty acids (SFCA), such as acetic acid and butyric acid, which are then absorbed by the host. Intestinal bacteria also play a role in synthesizing vitamin B and K as well as metabolizing bile acids, sterols and xenobiotics [8]. The systemic importance of the SCFAs and other compounds they produce are like hormones and the gut microbiota itself appears to function like an endocrine organ [8] and deregulation of the gut microbiota has been correlated with a host of inflammatory and autoimmune conditions [9].

From birth to death we change our diets which results in change in gut environment, therefore, the composition of human gut microbiota changes over the time, whenever diet changes, and as overall health changes [9]. A systematic review of 15 human randomized controlled trials from July 2016 found that certain commercially available strains of probiotic bacteria from the *Bifidobacterium* and *Lactobacillus* genera (*B. longum, B. breve, B. infantis, L. helveticus, L. rhamnosus, L. plantarum* and *L. casei*), when taken by mouth in daily doses of 109–1010 colony forming units (CFU) for 1–2 months, possess treatment efficacy (*i.e.*, improved behavioral outcomes) in certain central nervous system disorders – including anxiety, depression and autism spectrum disorder, and obsessive–compulsive disorder – and improved certain aspects of memory [10].

Certain probiotics showed efficacy in improving psychiatric disorder-related behaviors including anxiety, depression, autism spectrum disorder (ASD), obsessive-compulsive disorder and memory abilities, including spatial and non-spatial memory. According to the qualitative analyses of current studies, we can provisionally draw the conclusion that *B. longum, B. breve, B. infantis, L. helveticus, L. rhamnosus, L. plantarum* and *L. casei* were most effective in improving CNS function, including psychiatric disease-

associated functions (anxiety, depression, mood, stress response) and memory abilities.

Tryptophan metabolism by human gastrointestinal microbiota: IPA is a deamination product of tryptophan formed by symbiotic bacteria in the gastrointestinal tract of mammals and birds. IPA has been shown to prevent oxidative stress and death of primary neurons and neuroblastoma cells exposed to the amyloid beta-protein in the form of amyloid fibrils, one of the most prominent neuropathologic features of Alzheimer's disease. IPA also shows a strong level of neuroprotection in two other paradigms of oxidative stress [11]. *Lactobacillus sp*. convert tryptophan to indole-3-aldehyde (I3A) through unidentified enzymes [12]. *Clostridium sporogenes* converts tryptophan to Indole-3-propionate (IPA) [8], likely via a tryptophan deaminase. IPA also potently scavenges hydroxyl radicals. Production of IPA was shown to be completely dependent on the presence of gut microbiota and could be established by colonization with the bacterium *Clostridium sporogenes* [13]. IPA has previously been identified in the plasma and cerebrospinal fluid of humans, but its functions are not known. In kinetic competition experiments using free radical-trapping agents, the capacity of IPA to scavenge hydroxyl radicals exceeded that of melatonin, an indoleamine considered to be the most potent naturally occurring scavenger of free radicals. In contrast with other antioxidants, IPA was not converted to reactive intermediates with pro-oxidant activity (Fig.1).

Imbalance (dysbiosis) in microbiota population: Symbiosis equivalence to 'living in harmony' Dysbiosis is opposite; it's when the bad microbes take over. This phenomenon was first identified by Dr. Eli Metchnikoff in the early 20th century, who won a Nobel Prize for his work. It essentially means there is an imbalance of microbial colonies. This is most common in the digestive tract, but can happen anywhere in the body even the organs which are not covered with mucous membrane, such as the skin. Normally, bacteria maintain a harmonious balance in a healthy digestive tract by keeping each other in check so no one specific strain can dominate. What happens in a disturbed system is a strain's decreased efficiency at checks and balances. This can result in one colony becoming dominant and one becoming weaker. It instigates a chronic imbalance, debilitates and compromises our system as a whole. The beneficial bacteria are imperative. They help us with digestion, absorption, produce vitamins, control growth of harmful micro-organisms and keep the intestinal cells well fed by creating short chain fatty acids. Sometimes we simply need to reinforce the beneficial bacteria by recently evolved poop therapy [14] in order to get rid of the bad bacterial species. We can support them a great deal via nutrition and natural supplements. It's one of the first steps one can take to get a healthier GI tract and healthier skin, stronger immune system, more energy, better moods and likes.

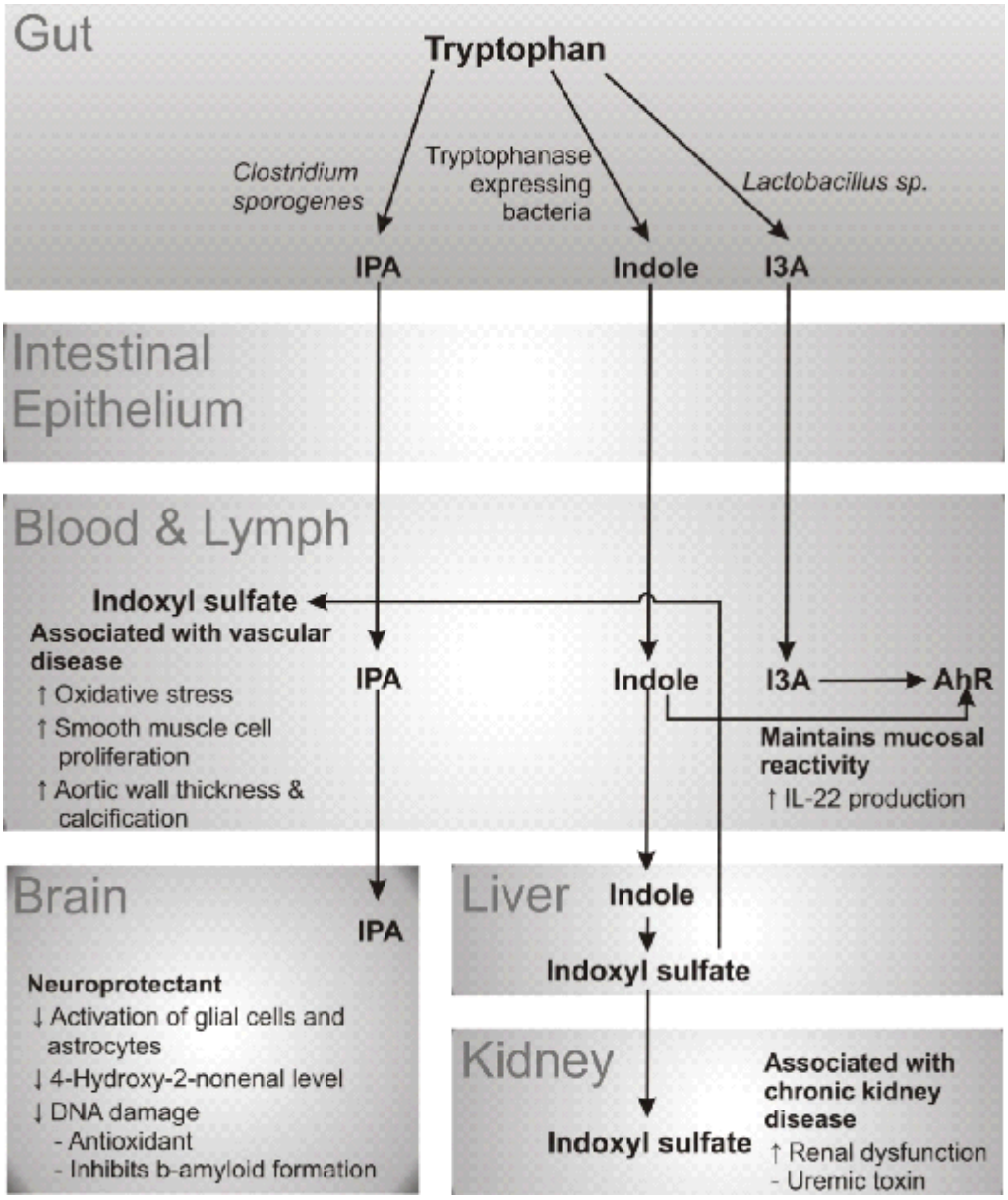
When dysbiosis exists, we may fall prey typically harmless microbes that can lead to serious health concerns. Elizabeth Lipski, cites dysboisis as a cause of arthritis, autoimmune illness, vitamin B deficiency, chronic fatigue syndrome, cystic acne, eczema, food allergies and food sensitivities, inflammatory bowel disease, irritable bowel syndrome, psoriasis and colon cancer [15].

Causes of dysbiosis: There are four major groups: fungus/yeast, parasites, viruses and pathogenic bacteria which when inhabits in the gut can cause imbalance in the beneficial colonies. The effects of alteration in the gut microbiota on the various organs are shown in figure 2.

Overseas travel and intake of contaminated food and water: Parasites are generally found in contaminated food and water and can be obtained during international travel. You can ingest contaminated food and water traveling or at home, as so much produce is brought in internation-ally. Viruses in the digestive tract are caught in the same way a common cold is, so better sanitation is your best defense, as antibiotics do not cure viruses.

Antibiotics: One of the most common causes of dysbiosis is from taking antibiotics. There are certainly times when antibiotics are absolutely necessary for your health, but the centre for disease control reports that antibiotics are grossly over-prescribed. The antibiotics kill off the bad bacteria, but they kill off all of the beneficial bacteria too - the gut flora that are keeping us armed with a healthy immune system. Every time a person takes antibiotics, sensitive bacteria are killed, but resistant germs may be left to grow and multiply. Over prescribing patients has caused antibiotic resistance, which is now one of the world's most pressing health problems. One must use own best judgment, spend time with doctor and ask questions about potential alternative

Fig. 1: Molecular mechanisms of action of indole and its metabolites on host physiology and disease.



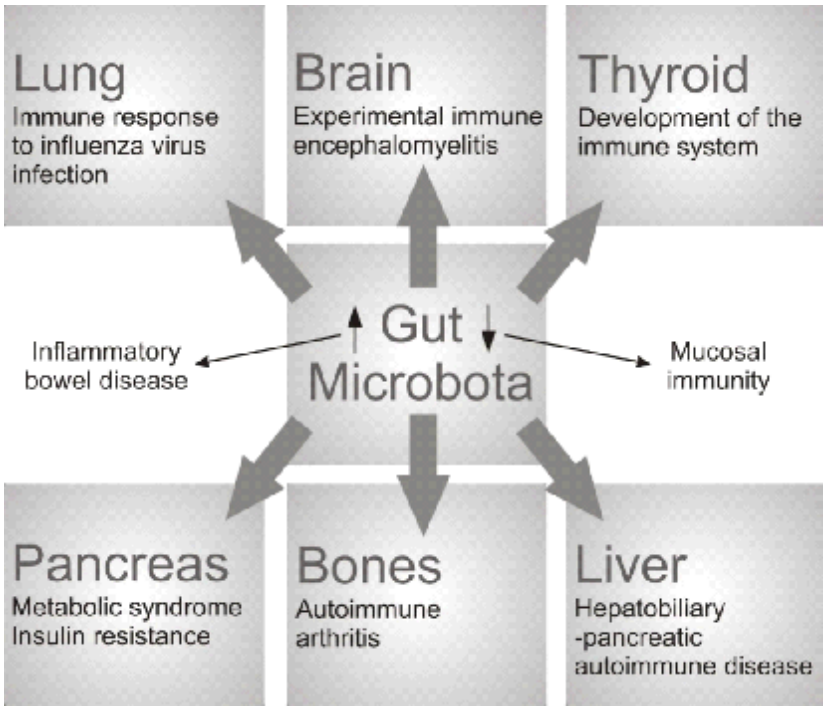
options when accepting an antibiotic regimen. Sometimes it is without a doubt imperative, other times one may have alternatives. If one has to do take antibiotics, make sure take a powerful probiotic during and after your medication round. One has to get antibiotics from the food you eat: just remember whatever that cow or chicken was given is being passed along to you. Be proactive with the food you eat and start thinking about where it came from [16, 17].

Increased use of NSAIDS: Abusing non-steroidal anti-inflammatory drugs (aspirin, advil, indomethacin, etc.) inhibits growth of healthy bacteria and can cause leaky gut, which can cause a bacterial imbalance [18, 19].

Incomplete or delayed digestion: Chronic constipation from a digestive disorder, such as inflammatory bowel syndrome or leaky gut, will contribute to the imbalance of microbiota [20].

Diet: An overgrowth of fungus and yeast can be caused by a diet high in refined carbohydrates and

Fig. 2: Effect of gut microbiota alteration on different organs of human body.



sugar. *Candida*, a type of yeast, is the most common condition caused by a sugary and starchy diet. *Candida* lives off of sugar. This means any sugar you eat feeds it. Remember that all starches that get broken down as sugar, including: grains, sugary fruit, starchy vegetables and lactose (sugar in milk). It's also important to make sure you get enough fiber in your diet, as diets high in protein but low in vegetables and fiber have been linked to dysbiosis. Most people have had success by overhauling their diet [21,22].

Elevated hormone levels: Pregnancy, use of hormone elevating drugs, including birth control and steroid hormones, can all spark an imbalance of gut microbiota. Chronic stress elevates stress hormones which will also wreak havoc on immunity, which makes more susceptible to an imbalance of gut microbiota [23].

Environment: Living in a damp, foggy climate, presence of mold or fungus in the home and exposure to toxic metals can increase susceptibility of getting non-friendly microbes (Smog, heavy metals, pesticides) [24].

Cancer and disbiosis: Communities of microbiota have been shown to change their behavior in diseased individuals. Although cancer is generally a disease of host genetics and environmental factors, microorganisms are implicated in H"20% of human malignancies (Table 1).

The association of various bacteria with gastrointestinal cancers. Mucosal microbes can become part of the tumor microenvironment (TME) of aerodigestive tract malignancies. Intratumoral microbes can affect cancer growth and spread. Gut microbiota also detoxify dietary components, reducing inflammation and balancing host cell growth and proliferation. Coley's toxins were one of the earliest forms of cancer bacteriotherapy. Refer to table 2 for effects of various microbiota related toxins on various cancers. Synthetic biology employs designer microbes and microbiota transplants against tumors [86].

Microbes and the microbiota affect carcinogenesis in three broad ways: viz,. 1. altering the balance of tumor cell proliferation and death, 2. regulating immune system function and 3. influencing metabolism of host-produced factors, foods and pharmaceuticals.

Modes of action: Ten microbes are designated by the International Agency for Research on Cancer

Table 1. Organisms responsible for gastrointestinal cancers. *H - evidence in humans; A - evidence in animal models; C - cell lines.

Bacteria	Cancer	*	Evidence	References
	Colorectal	A	Augments AOM-induced cancer in rats	25
	Colorectal	H	Increased prevalence of enterotoxigenic *B. fragilis* in human colorectal cancer	26
	Colorectal	A	Augments spontaneous (*Apc*$^{Min/+}$) and DMH-induced colorectal cancer in mice	27
	Gastric	A	Induces gastric cancer in gerbils	28, 29
	Colorectal	A	Infected cells induce tumors with high *H-ras* and *c-myc* expression in mice	30
B. vulgatus	Colorectal	A	Induces mild AOM-induced colorectal cancer in *Il10*$^{-/-}$ mice	31
Bacteroides fragilis	Colorectal	A	Enterotoxigenic *B. fragilis* augments *spontaneous* (*Apc*$^{Min/+}$) colorectal cancer in mice	29, 32
Bartonella sp.	General	A	Induces tumor-like structures and angiogenesis through VEGF	29, 33
Citrobacter rodentium and C. freundii	Colorectal	A	Etiologic agent of transmissible murine colonic hyperplasia	34
Escherichia coli	Colorectal	H	Increased mucosa-associated *E. coli* in human Crohn's and colorectal cancer	29, 35
H. felis	Gastric	A	Induces gastric cancer in insulin-gastrin transgenic mice	36
H. hepaticus + *H. bilis*	Colorectal	A	Dual infection induces colorectal cancer in *Mdr1a*$^{-/-}$ mice	37
H. pylori	Gastric	H	Causative agent of human peptic ulcer disease; Predisposes to gastric cancer	38, 39
H. typhlonius + *H. rodentium*	Colorectal	A	Dual infection in neonates induces colorectal cancer in *Il10*$^{-/-}$ mice	40, 41
Helicobacter hepaticus	Colorectal	A	Augments AOM-induced, and spontaneous colorectal cancer in *Smad3*$^{-/-}$, *Rag2*$^{-/-}$ and *Apc*$^{Min/+}$ mice	42 - 44
Lawsonia intracellularis	Proliferative enteropathy	A	Induces proliferative intestinal lesions in animals resembling human IBD lesions	45
Mycoplasma fermentans & M. penetrans	General	C	Induce malignant transformation and independence from growth factors *in vitro*	46 – 48
Streptococcus bovis	Colorectal	H	*S. bovis* bacteremia and endocarditis associated with human colorectal cancer	49 – 52

Table 2. Bacterial products linked to carcinogenesis.

Bacterial Toxins	Prominent Producers	Cancer Relevance	References
Bacillus fragilis enterotoxin	Enterotoxic *Bacillus fragilis*	Induces Stat3 activation and Th17 cells that promote colorectal tumorigenesis; Increased prevalence in human colorectal cancer patients	32, 53
Cytolethal distending toxin	*Helicobacter hepaticus*	Induces progression of hepatitis to dysplasia in mice	54
	Escherichia coli, Campylobacter sp., *Salmonella typhi*	Acts as a DNase to create double-strand DNA breaks; arrests host cell cycle at G2/M transition through inactivation of Cdk1	29, 55, 56
Cycle inhibiting factor	Enteropathogenic *E. coli*	Disrupts cell cycle through stabilization of Cdk inhibitors p21 and p27, cells replicate DNA without dividing, results in hyperploidy	57 – 59
Cytotoxic necrotizing factor	*E. coli*	Prevents apoptosis via Bcl-2 upregulation in epithelial cells; promotes motility in uroepithelial cells	60 – 62
Pasteurella multocida toxin	*Pasteurella multicida*	Promotes anchorage-independent growth of enterocytes and fibroblasts	63, 64
Epidermal differentiation inhibiting factor	*Staphylococcus aureus*	Induces transient hyperplasia in the epidermis of mice	29, 65
Cytotoxin-associated antigen A	*H. pylori*	Induces rapid progression through cell cycle and morphological changes that promote invasion; Augments the risk of human gastric cancer	66 - 68

(IARC) as human carcinogens. Most of these microbes colonize large percentages of the human population, although only genetically susceptible individuals develop cancer. Tumors arising at boundary surfaces, such as the skin, oropharynx and respiratory, digestive and/ urogenital tracts, harbor a microbiota, which complicates cancer-microbe causality. Substantial microbe presence at a tumor site does not establish association or causal links. Instead, microbes may find the tumor's oxygen tension or nutrient profile supportive. Decreased populations of specific microbes may also increase risks [86].

Human oncoviruses can drive carcinogenesis by integrating oncogenes into host genomes. Human *papilloma viruses* (HPV) express oncoproteins such as E6 and E7. Viral integration selectively amplifies host genes in pathways with established cancer roles [86].

Microbes affect genomic stability, resistance to cell death and proliferative signaling. Many bacteria can damage DNA, to kill competitors survive. These defense factors can lead to mutational events that contribute to carcinogenesis. Examples include colibactin encoded by the PKS locus (expressed by B2 group/ *Escherichia coli* as well as by other *Enterobacteriaceae* bacteria, *Bacteroides fragilis* toxin (Bft) produced by enterotoxigenic ***B. fragilis*** and cytolethal distending toxin (CDT) produced by several ε- and γ-proteobacteria. Colibactin is of interest in colorectal carcinogenesis, given the detection of PKS+ *E. coli*/ in human colorectal cancers and the ability of colibactin-expressing E. coli to potentiate intestinal tumorigenesis in mice. Data also support a role for enterotoxigenic ***B. fragilis*** in both human and animal models of colon tumors. Both colibactin and CDT can cause double-stranded DNA damage in mammalian cells. In contrast, Bft acts indirectly by eliciting elevated levels of/ reactive oxygen species/ (ROS), which in turn damage host DNA. Chronically high ROS levels can outpace DNA repair mechanisms, leading to DNA damage and mutations [86].

β-Catenin: Several microbes possess proteins that engage host pathways involved in carcinogenesis. The Wnt β-catenin/ signaling pathway, which regulates cells' polarity, growth and differentiation, is one example and is altered in many malignancies. Multiple cancer-associated bacteria can influence β-catenin signaling. Oncogenic type 1 strains of *Helicobacter pylori* express CagA, which is injected directly into the cytoplasm of host cells and modulates β-catenin to drive gastric cancer. This modulation leads to up-regulation of cellular proliferation, survival and migration genes, as well as angiogenesis all processes central to carcinogenesis. Oral microbiota *Fusobacterium nucleatum* is associated with human colorectal adenomas and adenocarcinomas and amplified intestinal tumorigenesis in mice. *F. nucleatum* expresses FadA, a bacterial cell surface adhesion component that binds host E-cadherin, activating β-catenin. Enterotoxigenic *B. fragilis*, which is enriched in some human colorectal cancers, can stimulate E-cadherin cleavage via Btf, leading to β-catenin activation. *Salmonella typhi* strains that maintain chronic infections secrete AvrA, which can activate epithelial β-catenin signaling and are associated with hepatobiliary cancers [86].

Several of these bacteria are normal microbiota constituents. The presence of these cancer-potentiating microbes and their access to E-cadherin in evolving tumors demonstrate that a loss of appropriate boundaries and barrier maintenance between host and microbe is a critical step in the development of some tumors [86].

Inflammation: Mucosal surface barriers are subject to environmental insult and must rapidly repair to maintain homeostasis. Compromised host or microbiota resiliency also reduces resistance to malignancy. Cancer and inflammatory disorders can then arise. Once barriers are breached, microbes can elicit pro-inflammatory or immunosuppressive programs [86].

Inflammation, whether high-grade as in inflammatory disorders or low-grade as in malignancies and obesity, drive a tumor-permissive milieu. Pro-inflammatory factors such as reactive oxygen and nitrogen species, cytokines and chemokines can also drive tumor

Table 4: Anticancer bacterial effect on the colorectal cancer.

Bacterial Spp.	References
Bacillus polyfermenticus	87, 88
Bifidobacterium spp., fe.	78, 89, 90
Bifidobacterium longum	91
Lactobacillus spp.:	77, 89, 90
Lactobacillus acidophilus	77, 90
Lactobacillus plantarum	77, 89, 90
Lactobacillus casei strain Shirota	77, 89, 91

growth and spread. Tumors can up-regulate and activate pattern recognition receptors (*e.g.* toll-like receptors), driving feed forward loops of activation of cancer-associated inflammation regulator NF-κcB . Cancer-associated microbes appear to activate NF-NF-κB signaling within the TME. The activation of NFNF-κB by/ *F. nucleatum*/ may be the result of pattern recognition receptor engagement or FadA enga-gement of E-cadherin. Other pattern recognition receptors, such as nucleotide-binding oligomerization domain–like receptor (NLR) family members/ NOD-2,/ NLRP3,/ NLRP6/ and/ NLRP12, may play a role in mediating colorectal cancer [86].

Immune system TME engagement is not restricted to the innate immune system. Once the innate immune system is activated, adaptive immune responses ensue, often with tumor progression. The interleukin-23/ (IL-23)–IL-17 axis, tumor necrosis factor–α/ (TNF-α) –TNF receptor signaling, IL-6–IL-6 family member signaling, and STAT3 activation all represent innate and adaptive pathways contributing to tumor progression and growth [86].

The microbiota adapts to host changes such as inflammation. Adaptation shift microbiota to a vulnerable tissue site. Genotoxin azoxymethane and colon barrier–disrupting agent dextran sodium sulfate independently results in colon tumors in susceptible mouse strains; combining them accelerates tumorigenesis [86].

Perturbations to a host immune system coupled with inflammatory stimulus may enrich bacterial clades that attach to host surfaces, invade host tissue, or trigger host inflammatory mediators. Fecal microbiota from NOD2- or NLRP6-deficient mice acquire features that enhance the susceptibility of wild-type mice to caCRC. In mice, gut microbiota modulate colon tumorigenesis, independent of genetic deficiencies. Germ-free mice developed more tumors when colonized from donors with caCRC, once followed by treatments that induced caCRC [86].

Testing for disbiosis: The myriad of dysbiosis symptoms can be overwhelming and very successful way to determine it is by *Candida*. A full health history that includes past use of antibiotics, chemical exposures, drug therapies, digestion habits and daily diet can pinpoint dysbiosis effectively.

A certified nutritionist can order tests that help determine the presence of *Candida*, which is often the culprit of dysbiosis. The urine organic acids - D arabinitol (a *Candida* metabolite and neurotoxin) is helpful in determining the presence of the yeast, *Candida*. The Comprehensive stool and digestive analysis test (CDSA) will give more comprehensive look at all the gut bacteria - including the presence of *Klebsiella, Candida,* bacterial balance imbalance, pathogenic bacteria, parasites, digestive abilities (absorption of nutrients) and gliadin antibodies (gluten) [86].

Researchers have been investigating differences between the gut microbiomes of healthy people and those who are sick to determine whether the gut microbiome enters a state of dysbiosis that contributes to disease. In a talk at the biology of genomes meeting (2017), Davenport described how she and her colleagues developed gut microbiome co-occurrence networks for thousands of people, some of whom were healthy and some of whom had conditions like asthma. Through their analysis, though, they found no consistent community differences in the microbial networks of healthy and sick people that held across various diseases. “There is no such thing as a healthy or disease state in the gut microbiome,” Davenport said [6].

Probiotic and genetically modified bacteria for prevention of cancer: Microbiotic activity has a significant impact on the health of the host. It affects the body at the local and system level. From the host’s point of view this can be a beneficial or detrimental effect, including: the nutritional status of the body, infections, metabolism of xenobiotics, toxicity of consumed chemicals or cancer processes. Refer to Table 3 for the list of anticancer effect of various bacteria on colorectal cancer. The role of intestinal microbiota and probiotics in the development of colorectal cancer has been analyzed. Experimental studies show that beneficial intestinal microbiota and its metabolic activity exert significant reductions in tumor lesions in the intestine. Several well-documented studies have been published that have shown significant inhibitory effects of lactic acid bacterial strains and bifidobacteria on early neoplastic lesions and further development of cancer in the small intestine of small animals. Studies on the effects of probiotics on etiology and growth of cancer in the human gastrointestinal tract are few. Nevertheless, some epidemiological and clinical data on experimental studies, mainly with healthy volunteers, indicate

significant antitumor activity of probiotics also in the human gastrointestinal tract. The mechanism of antitumor activity of probiotics has not been known. It is assumed that probiotics increase the pool of beneficial intestinal microbiota and inhibit the growth of pathogens, thereby altering metabolic, enzymatic, physicochemical, inflammatory and immunological activity in the intestine, thus limiting carcinogenic processes [92,93].

Probiotic bacteria are known to exert an anti-cancer activity in animal studies. *Bacillus polyfermenticus* (BP), a probiotic bacterium, has been clinically used for a variety of gastrointestinal disorders in East Asia. Conditioned medium of BP cultures (BP CM) inhibited the growth of human colon cancer cells including HT-29, DLD-1 and Caco-2 cells; suppressed colony formation of HT-29 cells and showed reduced tumor size in BP CM-injected mice when compared to *E.coli* conditioned medium-injected mice. The effect of BP CM appears to be medaited by ErbB2 and ErbB3. Moreover, cyclin D1 expression which is required for ErbB-dependent cell transformation and E2F-1 which regulates expression of cyclin D1 was decreased by BP CM. Taken together; the study suggests that this BP containing probiotic may be clinically used as a prophylactic treatment to prevent colon cancer development. In colorectal cancer, probiotic formulations have shown great promise as preventive and early stage therapeutics [92].

Probiotic characteristics are strain dependent and each probiotic needs to be tested to understand the underlining mechanisms involved in their beneficial properties. Genetic modification of lactic acid bacteria (LAB) was also described as a tool for new inflammatory bowel disease treatments. Studies show the efficacy of GM-LAB (using different expression systems) for the prevention and treatment of inflammatory bowel disease, highlighting the importance of the bacterial strain selection (with anti-inflammatory innate properties) as a promising alternative. These microorganisms could be used in the near future for the development of therapeutic products with anti-inflammatory properties that can improve the quality of life of inflammatory bowel disease patients [19,93].

The genetic modification of lactic acid bacteria as a tool to increase the anti-inflammatory potential of these microorganisms has also been demonstrated. The anti-cancer potential of different genetically modified lactic acid bacteria (GM-LAB) producing antioxidant enzymes (catalase or superoxide dismutase) or the anti-inflammatory cytokine IL-10 (protein or DNA delivery) was using a chemical induced colon cancer murine model. Dimethyl hydrazine was used to induce colorectal cancer in mice. The animals received GM-LAB producing anti-oxidant enzymes, IL-10 or a mixture of different GM-LAB. Intestinal damage, enzyme activities and cytokines were evaluated and compared to the results obtained from mice that received the wild type strains from which derived the GM-LAB. All the GM-LAB assayed showed beneficial effects against colon cancer even though they exerted different mechanisms of action. These mixtures of selected LAB and GM-LAB could be used as an adjunct treatment to decrease the inflammatory harmful environment associated to colorectal cancer, especially for patients with chronic intestinal inflammation who have an increased risk to develop colorectal cancer [94].

CONCLUSION

There are many causes of imbalance between beneficial and harmful bacteria. Mainly diet changes environment of the gut and due to which the balance between the two is disturbed. If this balance is not restored within a stipulated time either by therapy, withdrawal of antibiotics or other causes of killing beneficial bacteria then conditions develop for chronic diseases such as inflammatory and immunological diseases. Researchers have shown the involvement of this imbalance in developing gastrointestinal cancers.

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