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Review

Gut microbiome as a tumor promoter and tumor suppressor

Twinkle Yadav[1] · Raghav Syal[2] · Charu Tripathi[1*]

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Abstract

The human microbiome is the aggregate of all the microbiota that reside on and within the human body. They have the ability to affect the homeostasis of the host body and change its pathology by the production of various metabolites. There is complex crosstalk occurring between the gut microbiome and the host through the gut-brain axis. Gut microbiome plays a dual role in cancer by promoting as well as by inhibiting tumor formation. Tumor formation may be initiated by the release of certain metabolites which cause degradation and DNA breaks. However, a number of probiotic microbiota, residing in the gut can help prevent cancer initiation by provoking apoptosis in cancer cells, as well as increasing the efficiency of anticancer therapy and reducing its toxicity outcomes. Any imbalance in the microbiome composition leads to the alteration of the non-pathogenic potential of the microbiome and an increased risk of diseases in the host. Establishing a robust understanding of this interplay can be instrumental for understanding the factors leading to tumor formation. This review highlights the interplay between the host and gut microbiome, as well as the role of the gut microbiome in cancer prevention, tumor formation, and anticancer therapy.

Keywords

Microbiome, dysbiosis, cancer, antitumor therapy

Introduction

Microorganisms have been persisting on the surface of the earth since the beginning of life [1]. The co-evolution of multicellular organisms, eukaryotes, and microorganisms shows close interaction and relationships between them, including mutualism, commensalism, and parasitism. They depend on each other for the survival and maintenance of homeostasis [2, 3]. The human body has a 100-fold higher microbial gene composition than human genes [4]. Microbial genomes are a constitutive part of the host genetic substructure. Therefore, they affect the homeostasis of the body and change its pathology [5]. Gut microbiota refers to the diverse inhabitants of the gut, which include bacteria, archea, and viruses [6]. The microbiome residing in the gut has an extremely high impact on host homeostasis [7]. Among symbiotic microbial communities, gut microbiota plays an essential role in the production of vitamins, metabolism of dietary compounds, and protection against pathogens [8]. Therefore, any imbalance in the gut microbial equilibrium leads to the development of a condition known as dysbiosis. In a dysbiotic gut, altered microbial compositions lead to the decline of probiotic bacterial diversity. This leads to the expansion of pathogens among the microbiome, which is linked with the development of various pathological conditions [9]. The condition of gut dysbiosis comprises an increase in the percentage of small bowel bacteria and a change in the relative percentage of microbial pathogens. The development of a disease state is fundamentally influenced by a variety of components, such as microbial interactions, microbial metabolites, host immune response, host physiology, food, and host environment [10]. The most common phyla in the gut of a healthy host are *Bacteroidetes* and *Firmicutes*, while the *Proteobacteria*, *Actinobacteria*, *Fusobacteria*, and *Cynobacteria* are only found in trace amounts [11]. Intrinsic and extrinsic variables have a significant role in the development of small intestine bacterial overgrowth (SIBO) [12]. Typical gut defence mechanisms, gastric acid and bile acid secretion, the synthesis of mucin, gut antibacterial peptides, peristaltic movement, and mitigation of bacterial retrograde translocation from the lower gut to the upper gut through the ileocecal valve are the most known intrinsic factors that inhibit the overgrowth of bacteria [13]. However, nutritional intake, infections and drugs which alter mobility and modify gut resident microorganisms are examples of extrinsic influences [14]. Any imbalance in the extrinsic factors leads to the colonization of pathogenic bacteria in the gut. SIBO has been linked to a number of difficulties among affected hosts including the loss of microvilli, the induction of epithelial inflammatory response, impaired fat absorption, and an inadequate supply of the fat-soluble vitamins D, E, A and K [15].

In the past few years, there has been an unprecedented advancement of metagenomics and next generation sequencing, leading to an accelerated pace of computational analysis of 16s rRNA amplicons to identify the diversity and abundance of the gut microbiome. Progress in metagenomics studies, along with simultaneous advancements in transcriptomics and metabolomics, has helped in understanding the impact

[1] Department of Zoology, C.M.P. College, University of Allahabad, Prayagraj, India.
[2] St John of God Midland Public and Private Hospital, Western Australia, Australia.

*Corresponding author: charutripathi89@gmail.com

of individual microbial species on host health [16, 17]. Microbiome studies can be performed by amplicon sequencing or shotgun sequencing. In both the techniques, the genomic DNA of the microbial community is isolated. In the case of amplicon sequencing, the 16S rRNA gene of the community gDNA is amplified by PCR and sequenced, whereas, in the case of shotgun sequencing, the total genomic DNA is fragmented and sequenced. In both methods, OTUs are clustered based on their similarity to sequences in the database. Alpha diversity (within sample diversity) and beta diversity (inter-sample diversity) are elucidated in both cases using varied statistical techniques such as Shannon indices, principal component analysis, rarefaction analysis and other statistical analyses (figure 1). Further, community functional profiles can be generated from shotgun sequencing data which are used for building metabolic models and assigning roles to bacterial members in a complex community.

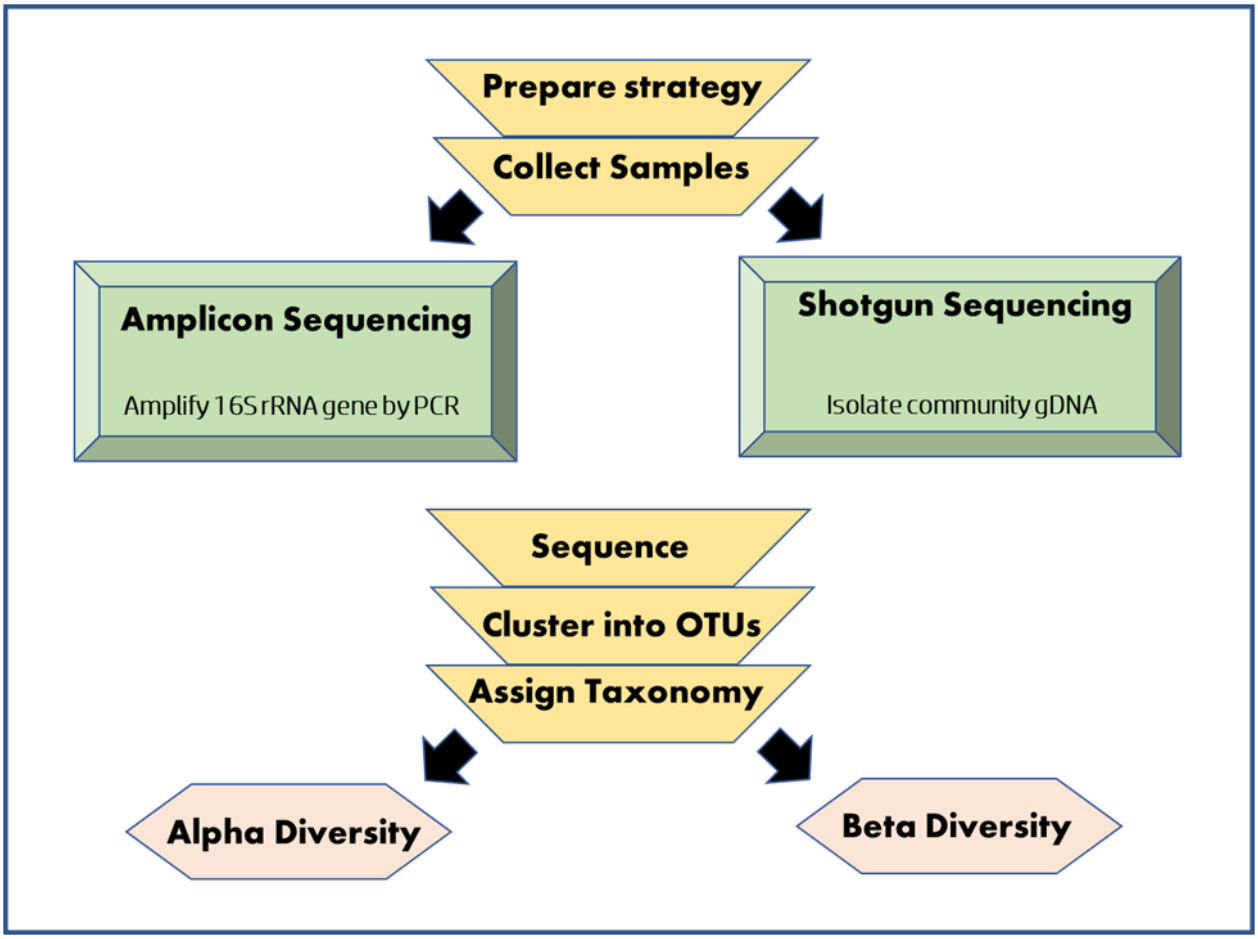

Figure 1: Overview of methodology for performing a microbiome study.

Efforts to understand the composition and roles of the microbiome have been underway for more than a decade now. The Human Microbiome Project (HMP) has highlighted the characteristic microbiome composition at varied sites in the healthy human body throughout the US population [18]. Following that, the Metagenomics of the Human Intestinal Tract (MetaHIT) project sought to better understand the gut microbiome and its interactions in European populations [19]. This led to the understanding that sometimes some microbes (known as “alpha bug”) can alter the delicate balance of the community by exploiting resources for their own benefit. This can cause a disruption in gut composition, resulting in “dysbiosis,” a condition associated with and contributing to inflammation. Inflammation and dysbiosis-associated chemical compounds such as N-nitroso and acetaldehyde (produced from alcohols) are generated as a result of bacterial metabolism, leading to dysplasia, and have been implicated with carcinogenesis [20]. For conducting microbiome studies, the gut microbiome is sampled by collecting oral and fecal samples, whereas other tissue samples may be collected for specific studies. Differences in oral and fecal samples denote the transition in the gut microbiome, highlighting the diverse roles played by the microbiota at specific niches.

A number of recent studies have revealed the pivotal role of commensal bacteria colonizing the body surface as a cause of healthy or pathogenic conditions such as cancer [21, 22]. Tumor formation is one of the critical conditions that has been identified as the world's second-leading cause of death [23]. Spontaneous

mutations during DNA replication, environmental exposure, and certain lifestyle alterations are some of the factors influencing the risk of cancerous growth. Studies in the fields of metagenomics and metabolomics have revealed that the gut microbiome plays a pivotal role in the formation of cancer (tumorigenesis) as well as in the prevention of cancer [24]. A robust understanding of the interplay between host-gut microbiota and maintenance of homeostasis has aided a number of research groups to apply this knowledge to the augmentation of anticancer therapies aimed at restoring a balanced gut microbiome and thus a balanced gut function [24]. In this review, we have highlighted the recent studies which establish the association between gut microbiota and tumor formation or prevention. Apart from this, the application of probiotics in anticancer therapy has been discussed.

Gut microbiota and host interaction

It has been established that there is intricate interaction between the host and its microbiota. Recently a number of research groups have identified the approaches by which microorganisms influence their host and are themselves influenced by the host [25]. This complex crosstalk that occurs between the host and its microbiota consists of the host central nervous system, autonomic nervous system, enteric nervous system, hypothalamic-pituitary adrenal axis, and entero-endocrine system. This interaction is collectively referred to as the gut brain axis [26] through which, the gut is bidirectionally linked with the nervous system. Several hormones and neurohormones are secreted by gut brain axis which have the potential to change the tone of digestive system and metabolic activity [27] and modify the gut microbiome composition [28]. Various hormones and peptides secreted by the gastrointestinal entero-endocrine cells are involved in several functions, including intestinal motility, digestion, as well as neural modulation of the host [29]. Microbial inhabitants of the gut are able to sense the hormones and neurohormones secreted by the host. The gut microbiome composition is thereby influenced by these factors as well [30]. Similar to the host gut brain axis, gut microbiota also secretes certain microbially derived metabolites or active molecules that are able to affect the host gut brain axis [28]. These molecules directly or indirectly affect the host health and functions by influencing the metabolism, altering its drug metabolism and modulating the immune system function (table 1) [31]. Some commensal bacteria secrete molecules known as micronutrients, such as vitamin K and vitamin B. Specifically, short-chain fatty acids are bacterially-derived metabolites which have been shown to play a role in glucose and lipid metabolism by impacting the intestinal peptide hormone secretion and its synthesis, depending on the host diet and microbial composition of the gut [32]. Current studies have revealed that protein-protein interactions occur between the intestinal microbiome and its host. Structural insights into proteins from commensal and probiotic bacteria have revealed that host binding functions of proteins from beneficial bacteria are able to regulate the host physiology [33]. The complex interaction between the host and its resident microbial community is thus a key factor for determining the host health and transition to disease state.

Table 1: Mode of synthesis and biological functions of microbial metabolites.

Microorganisms	Microbial metabolites	Mode of Synthesis	Functions	References
Blautia hydrogenotrophia and other enteric bacteria	Acetate	Wood-Lijungdahl and acetyl CoA pathways.	Receptors like G protein-coupled receptors (GPCRs) GPR41, GPR43, and GPR109A may recognize one of the short-chain fatty acids, and acetate on the surface of the immune cells and colonocytes.	[34]
Firmicutes	Butyrate	Derived from acetyl CoA.	Gut epithelial cells use it as a source of energy. Additionally, it prevents colonocytes and immune cells from producing histone deaceytlase, which encourages hyperacetylation of histone.	[34]
Bacteroidetes	Propionate	Succinate pathway	It prevents colonocytes and immune cells from over-acetylating histone by inhibiting the activity of histone deaceytlase.	[34]
Bacteroidetes	N-nitoso compounds (NOCs)	Synthesized endogenously through acid-driven nitrosalation by	Causes mutations in DNA by DNA alkylation.	[35]

Microorganisms	Microbial metabolites	Mode of Synthesis	Functions	References
		nitrosation of amines obtained from microbial protein fermentation in the large intestine.		
Ruminococcus gnavus and *Clostridium sporogenes*	Tryptamine	Gut bacteria synthesize tryptamine from tryptophan.	Promotes fluid secretion across the colonic epithelium.	[35]

Gut microbiome and tumor suppression

The gut microbiome can suppress tumor formation by producing several molecules with anti-tumor activity. Specifically, short-chain fatty acids produced by microbiota have an antitumor effect on mucosal cells by promoting cell cycle arrest and apoptosis in transformed mucosal epithelial cells [36]. Apart from this, butyrate and propionate are gut bacterial molecules that are capable of inhibiting host tumor cell histone deacetylases [37], leading to altered DNA – histone structural framework in tumor cells, which brings about apoptosis or cell cycle arrest [38]. Furthermore, butyrate reduces inflammation in the mucosa by inhibiting INF/STAT signaling. Cytokine INF is secreted in inflamed mucosa. Inhibition of INF signaling has been shown to reduce inflammation in the mucosa [36].

Modulation of the immune system is one of the key strategies to inhibit tumor development. Host microbiota secretes some molecules that modulate the host immune system or enhance the activity of immune cells against cancer. Lipopolysaccharide, an outer membrane component of gram negative bacteria, is a well studied bacterial molecule that activates toll-like receptor 4 (TLRs), a pattern recognition receptor in gut cells. TLRs activate T cells against transformed cells, cancerous cells, and virus infected cells [39]. In the same way, pyridoxine produced by bacteria can influence the host immune system against tumors [40] by enhancing the proliferation of blood and spleen lymphocytes, thereby activating the immune response [41]. Moreover, it acts by reducing the levels of oncogenic cell proliferation proteins c-myc and c-fos in colonic crypts [42]. The probiotic metabolites produced by *Lactobacillus ceasei* influence apoptosis of tumor cells by activation of the JNK pathway [43]. Additionally, natural killer cells and dendritic cells are stimulated by *Lactobacillus*, which are attributed to the destruction of transformed or tumor cells. Recent studies on mice and humans revealed that *L. reuteri* reduces colorectal cancer by increasing tumor reactive oxygen species and decreasing protein translation. [44]. Even though a number of such molecules have been identified, however a number of bacterially derived byproducts that stimulate immune responses still need to be identified.

Neoplasm growth retardation and tumor elimination have been demonstrated in malignancies by the invasion and colonization by *Lactobacillus, Shigella, Clostridia, Listeria, Vibrio Bifidobacteria, Escherichia* and *Salmonella* [45]. Additionally, some bacterial genera, such as *Bifidobacterium longum* and *Clostridium* strains, have been shown to colonize and thrive in the low-oxygen state in which tumor cells grow and have been shown to eradicate these cells [45]. Studies have linked *E. coli* to the induction of cytotoxic T cell response, which is responsible for generating INF-Y and enhancing the expression of MHC Class-I on the tumor cells, leading to a greater attraction of CD8+ T cells to the tumor cells leading to a greater degree of tumor suppression [45]. Moreover, there are some bacterially derived substances which have anticancer activity including, bacteriocin, bacterial peptides and bacterial toxins. Bacteriocin produced by *Streptococcus bovis* known as bovicin HC5, inhibits the growth of breast, hepatocellular, and hepatic cancer cells by bringing about potassium efflux and pore formation in these cells. Apart from this, a variety of enzymes synthesized by bacteria have anticancer activity. One of the enzymes secreted by *Mycoplasma hominis* known as arginine deminase has specific anticancer action. This enzyme inhibits cell growth, triggers autophagy, amino acid depletion and induces caspase-independent apoptosis in tumor cells [46]. Bacterial peptides such as azurin and P28 produced by *Pseudomonas aeuriginosa* have also been shown to have antitumor properties in melanocytes, liver cell lines, colon cell lines, and breast cancer cells [47]. Additionally, some bacterial toxins have been demonstrated to have antitumor properties. For instance, the exotoxin diphtheria toxin from *Corynebacterium diphtheria* inhibits the growth of tumor cells by binding to heparin-like growth factors, reducing angiogenesis, and triggering cell death. Moreover, Exotoxin A and Exotoxin T produced by *Pseudomonas aeuriginosa* reduce tumor growth by bringing about apoptosis in cancer cell lines [48].

Gut microbiome and tumor progression

Diet is one of the critical factors determining the composition of microbial diversity. A study compared the gut microbiomes of a population of rural Africans, whose diet comprise higher resistant starch (similar to soluble fermentable fiber) intake with Americans whose main dietary components are meats and fats. Rural African diet promotes the formation of short-chain fatty acids like butyrate and aids in proliferation of beneficial bacteria in their gut which inhibit cell proliferation and trigger apoptosis by inhibiting histone deacetylases. Africans thereby displayed a lower risk of colorectal cancer when compared to Americans [49]. This difference is due to the distinction in the composition of microbes and their metabolites between the two populations. This study revealed that Africans harbored more of *Prevoltella* spp. and butyrate was the predominant metabolite generated, while Americans had plentiful *Bacteroides* spp. and the major metabolites generated were secondary bile acids.

Since diet selection can alter the composition of microbiomes [49], within a dysbiotic gut, several pathogenic bacteria disturb the host metabolism and immune system function. Minute disturbances in cell cycle regulation can influence tumor formation and expansion (figure 2) [50]. These conditions are mostly associated with the colon, gastric region, esophagus, pancreatic and gall bladder carcinomas. Gastrointestinal dysbiosis affects local as well as distinct tumors [51]. A shift in microbial composition can cause 20% of tumor development and a variety of malignancies [49]. To understand how the gut microbiome is involved in cancer development, several studies have been performed on mice models which have revealed that inflammation changes the gut microbial composition in colitis susceptible IL-10 deficient mice [52]. Apart from this, colonization of *E. coli* in the gut promotes invasive carcinoma in azoxymethane treated mice [52].

Cancer has been linked to prolonged inflammation. To understand the association of inflammation and gut microbiome in the development of colorectal cancer, many hypotheses have been proposed. According to the alpha bug hypothesis, colonic microbiota are remodeled by entero-toxigenic *Bacteroides fragilis* by IL-17 and TH17 cell mediated inflammation. Altered microbiomes enhance the host susceptibility to the pathogens [49]. Some metabolite byproducts produced by the altered microbiome, including secondary bile acids, prostaglandin E2 and short-chain fatty acids can determine the initiation and progression of tumors [53].

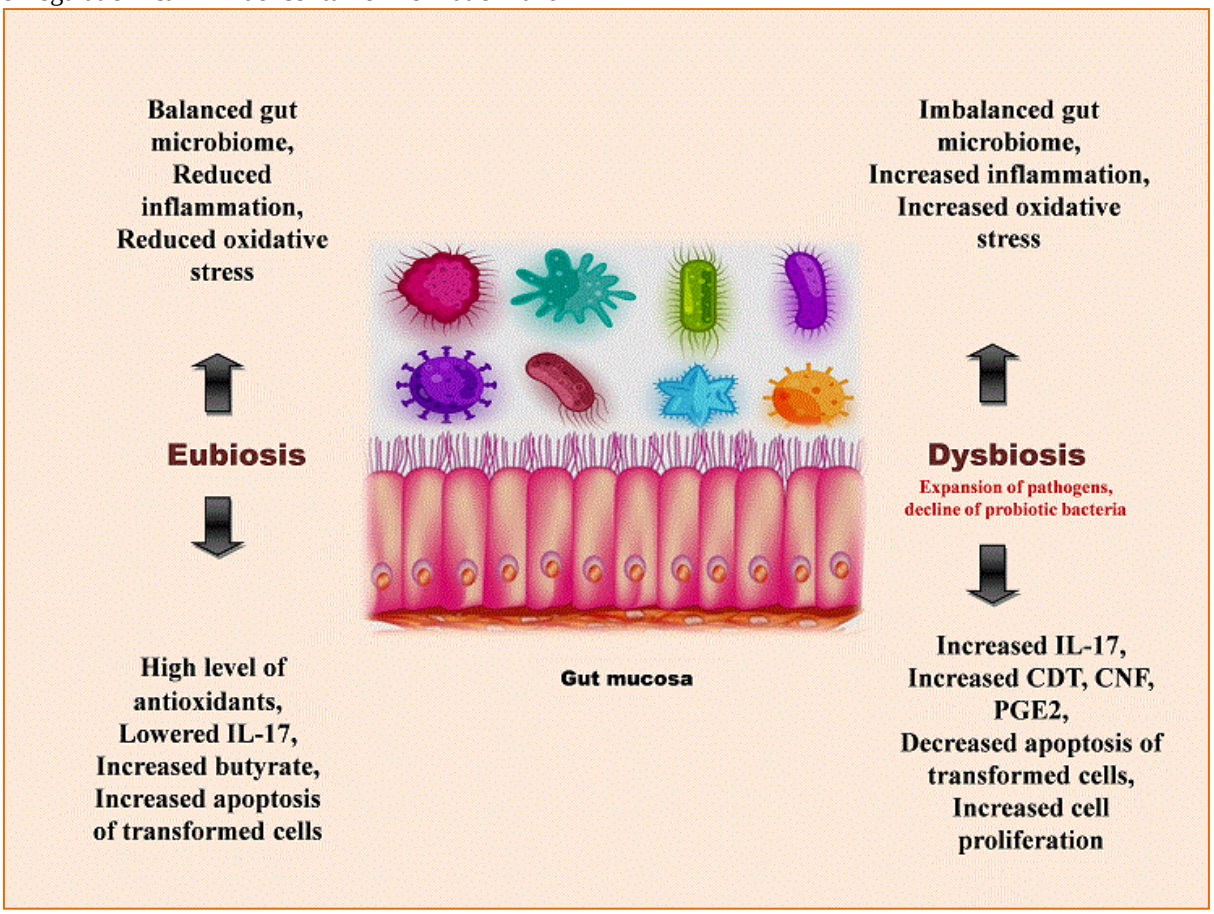

Figure 2: Schematic representation of differences between eubiotic and dysbiotic gut mucosa. Progression from balanced state to an imbalanced state involves changes in metabolites/molecules produced by gut residents.

Gut microbiota have the potential to influence oncogenesis by many molecular mechanisms, including reactive oxygen species (ROS) production, interference with gut permeability through inflammation and mucin degradation, as well as DNA damage and initiation of aberrant signaling pathways [49]. Cytotoxin associated gene A (CagA), a protein produced by *Helicobacter pylori,* a resident in the mucus layer of the stomach, has been found to be associated with gastric cancer [26]. The CagA protein causes abnormal beta-catenin activation, apical junctional complex disruption by targeting the cell adhesion protein E-cadherin, and cellular polarity loss [54]. Pathogenic bacteria in the dysbiotic gut produce genotoxins, which cause breaks in the host DNA [55]. Production of DNA damaging genotoxins has been identified in *E. coli, Aggregatibacter, Haemophilus duceryi, Shigella dysenteriae,* and *Campylobacter jejuni* [56]. Cytolethal distending toxin (CDT) and colibactin, produced by *E. coli* in the gut epithelium, have DNAse activity. These toxins introduce double stranded DNA breaks in the host epithelium cells, leading to mutation and an increased probability of tumorigenesis [57] (figure 3). A number of studies based on cell culture and animal models have also described the potential of other microbes, namely *Helicobacter pylori, Pseudomonas aeruginosa,* and the uropathogenic strain of *E. coli,* that affect DNA replication of the host, in addition to known production of genotoxins (table 2) [56]. Apart from this, some residents of the gut, such as *Shigella flexneri,* are involved in altering DNA damage responses and repair pathways in the host by secreting inositol phosphate phosphatase D (IpgD) and cysteine proteases which induce the degradation of the p53 tumor suppressor protein [58]. The degradation of p53 is also brought about by the CagA protein produced by *Helicobacter pylori* in the gastric epithelium [59].

Gut microbiota can enhance the probability of cancer formation by altering the cellular signalling pathways of the host. In particular, several bacterially-derived products, such as *Fusobacterium nucleatum* effector adhesin A (Fad A) and *Bacteroides fragilis* metalloproteinase toxin (MP toxin) act on the host epithelial E-cadherin and disrupt intracellular junctions, activating β-catenin pathway, that leads to the alteration of cell cycle regulation, enhancing cell proliferation and leading to tumor formation in affected host cells [60]. Additionally, avirulence protein A (AvrA) produced by the *Salmonella enterica* has intrinsic deubiquitinase activity which suppress the β-catenin ubiquitination and inhibits its degradation in intestinal epithelial cells [61]. The gut microbiome can also induce tumor development by generation of ROS and genomic mutation in cells [62]. Microbes such as *Helicobacter pylori* and *Bacteroides fragilis* have the ability to activate the host spermine oxidase which acts as a ROS and ultimately brings about DNA mutations [63]. Similarly, extracellular superoxide and derivative oxygen species produced by *Enterococcus faecalis* diffuse into the host cells, increasing the ROS which triggers cellular DNA mutation [64].

Modulation of the host immune system is one of the key strategies used by the host microbiota to promote disease development in the host. Immune cells that typically prevent tumor development are hindered by pathogenic microorganisms. In particular, *Fuscobacterium nucleatum* employs virulence factor Fap2 to inhibit NK cells and thus interferes with the NK cell-mediated tumor cell attack [65]. Similarly, a lipopolysaccharide derived from *Klebsiella pneumoniae,* brings about tumor initiation by targeting the host tumor suppressor p53 pathway through mRNA destabilization [66]. Additionally, by positively or adversely affecting the regulation of cell proliferation, inflammation, and death, metabolites produced by the microbiome (oncometabolites) can play a crucial role in regulating the tumor microenvironment. Recent studies have demonstrated that oncometabolites contribute to the epithelial-mesenchymal transition, which supports the development of the metastatic niche [67]. They can aid in the growth and development of tumors because they are produced and stored in cancer cells as a result of abnormal metabolism [68]. Cancer cells have an altered metabolism, which helps them grow, survive, and combat therapy [69]. Bacterial metabolites including prostaglandin E2, multiple short-chain butyrate acids, and secondary bile acids are associated with the risk of cancer [70]. Diet is one of the primary factors directly and indirectly influencing the production of metabolites in the gut. High fat diets promote an increase in the production of secondary bile acids, (such as deoxycholic acid) which are associated with colonic inflammation and increased risk of cancer development [71]. Although most of the primary bile acids are reabsorbed by enterohepatic circulation, some primary bile acids are biotransformed by resident bacteria into secondary bile acids in the colon.

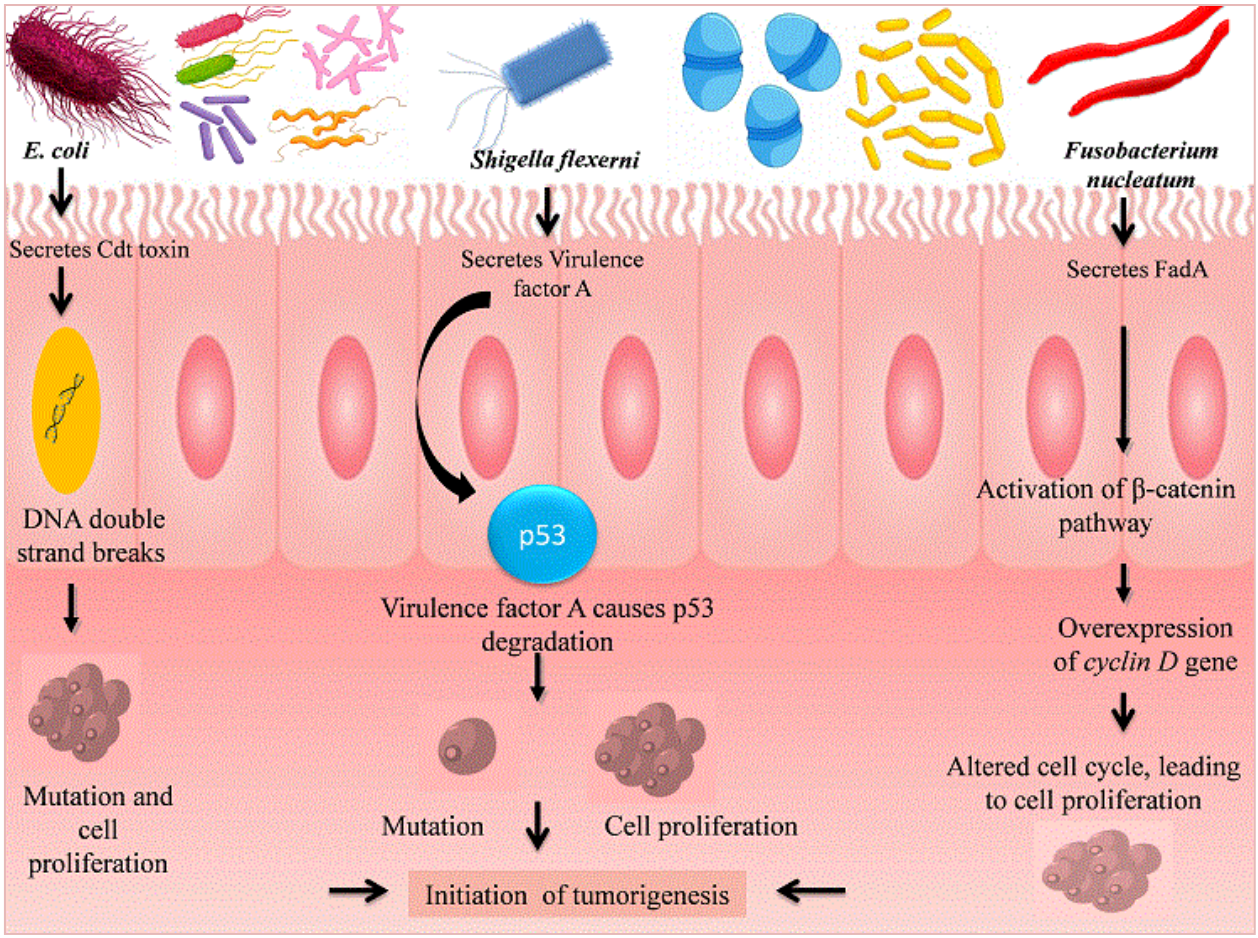

Figure 3: Microbially derived toxins and their pro-tumoral effects on the host cell cycle regulation and DNA repair pathways which ultimately transform normal mortal cells into immortal cancerous cells.

Table 2: A list of microbial candidates associated with different cancers and factors which promote tumor formation and progression.

Microorganisms	Cancers	Factors promoting tumor formation and progression	References
Helicobacter pylori	Gastric cancer	(i) Production of cytotoxin Cag A and generation of vacuolating cytotoxin A (VacA), which activates the mitogenic Ras extracellular signal regulator kinase pathway and the oncogenic phosphatidyl inositol 3 kinase (PI3K) pathway, resulting in the disruption of cell generation, cell cycle, and cell death.	[72], [73]
Neisseria gonorrhoea	Ovarian cancer and urinary bladder cancer	(i) Modifying the expression of cyclin B and halting the cell cycle in the G1 phase. (ii) Increased expression of amphiregulin, which promotes tumor formation by interfering with critical cell processes and causing unrestricted cell proliferation, angiogenesis, and apoptosis resistance.	[74]
Salmonella tymphimurium	Hepatobiliary carcinoma and colon cancer	(i) Alteration of the host cell signalling pathways such as, AKT and ERK pathways. (ii) Activation of the host β-catenin pathway through the release of the effector AvrA.	[75]

Microorganisms	Cancers	Factors promoting tumor formation and progression	References
Chamydia trachomatis	Squamous cell carcinoma, cervical cancer and ovarian cancer	(i) Degradation of proapoptotic protein BH3. (ii) Upregulation of antiapoptotic proteins. (iii) p53 degradation. (iv) Establishment of *myc* oncogene.	[76]
Campylobacter jejuni	Small intestinal lymphoma and gastrointestinal tract cancer	(i) Generation of cytolethal distending toxins which have DNAse activity that can disrupt double-stranded DNA.	[77]
Porphyromonas gingivalis	Oral squamous cell cancer, gastric cancer hepatocellular cancer and oesophageal cancer	(i) Altering metabolic processes by triggering inflammatory response and preventing apoptosis. (ii) Increases the levels of matrix metalloproteinase-9 and stimulates the P38/HSP27, PAR2/NF-KB, and ERK1/2 Ets1 pathways, which facilitate cellular invasion.	[78], [79]

Role of gut microbiome in anticancer therapy

The microbial composition not only affects the health and well-being of the host but has also been shown to promote or reduce the outcomes of anticancer therapy via modulation of drugs. Previous research has shown that gut microbiota can influence the efficacy of anticancer drugs used in conventional chemotherapy, such as oxalipantin, a platinum-derived drug used in gastrointestinal tumors [80]. Specifically, microbes such as *E. coli*, *Staphylococcus*, *Lactobacillus*, *Bifidobacterium*, and *Clostridium* have been shown to enhance the efficacy of oxaplatin against tumors by inducing ROS release from myeloid cells to provoke apoptosis in cancer cells. Furthermore, cyclophosphamide (CTX) drugs used to treat hematological malignancies and solid tumors have an antitumor effect associated with the translocation of selective gram-positive bacteria from the small intestine to the secondary lymphoid organ, where helper T cells can be activated (table 3). However, some microbes like *Fusobacterium nucleatum* downregulate the efficacy of the 5-fluorouracil drug, which is used in colorectal cancer [80].

Table 3: Role of resident microbiota in enhancing the efficacy of anticancer therapy.

Microbes	Effect on anticancer therapy	References
Escherichia coli, Stapylococcus, Clostridium	Reduced the side effects of the anti-cancer drug irrinotecan.	[80]
Mycobacterium obuense	Stimulate cytotoxic and antigen-presenting cells to initiate the anticancer immune response.	[81], [82]
Lactobacillus johnsonii	The antitumor molecule cyclophosphamid, when employed with *Lactobacillus johnsonii*, leads to the transformation of naive T cells into proinflammatory T helper 17 (Th17) cells.	[83]
Alistipes shaii	Restores TNF production to boost the outcome of the therapy.	[84]
Bacteroides fragilis, Burkhoderia cepacia	Enhance the effectiveness of anti-CTLA4 antibodies, which suppress the development of sarcoma tumors.	[85]
Bifidobacterium	Combined with anti-PD-L1 antibody, T cell responses are enhanced and melanoma growth is inhibited.	[86]
Akkermansia muciniphila	Boosts cytotoxic T cell infiltration into cancerous tissues.	[87]

Microbes	Effect on anticancer therapy	References
Enterococcus faecium	Enhance anti-PD-L1 efficacy.	[88]
Burkholderia, Bacteroides fragilis	Reduce the cytotoxic side effects of immunotherapy.	[85]

The microbiome also affects cancer therapy by its ability to metabolize antitumor compounds and modulate immune responses [89]. Therefore, these microbes can also affect the outcomes of immunotherapy. Crosstalk between the immune checkpoint molecules that are present on the tumor cells and their receptors on immune cells is associated with the immune defense system of the host against tumor. Antitumor immunity is influenced by the administration of the antibodies against programmed death-1 (PD-1) protein, programmed death ligand (PDL-1) protein, and CTLA-4 present on T lymphocytes [55]. Previous research using metagenomics and fecal sample studies demonstrated that the microbiome composition of cancer patients with an anti-PD-1 responder microbiome differs from that of non-responders [90]. Apart from this, anticancer therapy along with anti-PD-1 administration has been shown to enhance the outcome of treatment in mice. Moreover, a recent study revealed that modification of the host microbiome could enhance the efficacy of immunotherapy. It has the potential to be used as a biomarker for regulating and improving therapy outcomes, mainly in CTLA-4 and anti-PD-1-treated patients [91]. Additionally, some bacterially-derived molecules such as monophosphoryl lipid A, produced by *Salmonella enterica* enhances the effects of therapy and is being used as an adjuvant in vaccines that are being developed against cervical carcinoma [92]. In addition, rifaximin, when combined with probiotics, enhanced the anti-inflammatory activity of rifaximin in the rat model of inflammatory bowel disease [93].

Impairment of the fundamental cellular processes of the host leads to the initiation and progression of tumor. A single cancer cell might develop into tumors having multiple clones of tumor cells, therefore, each cancer cell might respond differently to anticancer therapies [94]. These variations in tumor cell populations are connected with the resistance to anticancer therapy [95]. To overcome this resistance, specific genetic features of malignancies based on the personalized approach are under development [96]. It is well studied that radiotherapy, chemotherapy, and immunotherapy treatments modulate the host microbiome composition as well as the host's response to therapy. Almost every anticancer therapy has toxic effects on normal cells apart from the cancer cells, but microbial interventions can reduce the anticancer drug-related toxicity [97, 98].

Conclusion

A complex interaction occurs between the microbiome and its host in which they affect each other in numerous ways. The microbiota has an enormous metabolic capability. It is well known to have a variety of effects on human health and disease susceptibility. A balanced microbiome contributes to maintaining human health. However, any imbalance in gut microbiota composition leads to dysbiotic gut conditions that might lead to inflammation and other aberrant conditions such as tumors. The microbiome also plays a role in increasing the efficacy of antitumor therapy, as well as in reducing their toxic outcomes. However, as we gain more knowledge about the gradient from eubiosis to dysbiosis, we can create strategies to manipulate the gut microbiota to benefit health. Presently, advancements in next-generation sequencing, metagenomics, metatranscriptomics, and metabolomics provide an opportunity to identify the diversity and composition of the gut microbiome as well as allow us to understand the functional interactions among them and with the host. Even with the ongoing research, the precise microbial metabolites involved in tumor suppression still remain unidentified and the functional properties of the gut microbiota remain poorly understood. Further investigation of these aspects has the potential to revolutionize medical treatments in the future.

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Declarations

The authors declare that there is no conflict of interest.

References

1. Dzustv A, Badges HJ, Chanona Perez E, Roy S, Salcedo R et al(2017) Microbes and cancer. Annu. Rev. Immunol 35:199-228. https://doi.org/10.1146/annurev-immunol-051116-052133

2. Yutin N, Wolf MY, Wolf YI, Koonin EV (2009) The origin of phagocytosis and eukaryogenesis. Biol Direct 4:9. https://doi.org/10.1186/1745-6150-4-9

3. McInerney JO, Connel MJ, Pisani D (2014) The hybrid nature of the eukaryota and a consilient view of life on earth. Nat Rev Microbial 12:449-455. https://doi.org/10.1038/nrmicro3271

4. Hugenholtz F, de Vos, WM (2018) Mouse models for human intestinal microbiota research: a critical evaluation. Cell Mol Life Sci 75: 149–160. https://doi.org/10.1007/s00018-017-2693-8

5. Candela M, Biagi E, Maccaferri S, Turroni S, Brigidi P (2012) Intestinal microbiota is a plastic factor responding to environmental changes. Trends microbiol 20:385-91. https://doi.org/10.1016/j.tim .2012.05.003

6. Lynch SV, Pederson O (2016) The human intestinal microbiome in health and disease. N Engl J Med 375: 2369-2379. 10.1056/NEJMra1600266

7. Feng Q, Chen WD, Wang YD (2018) Gut microbiota: An integral moderator in Health and Diseases. Front Microbial 9:15. https://doi.org/10. 3389/fmicb.2018.00151

8. Belkaid Y, Naik S (2013) Compartmentalized and systemic control of tissue immunity by commensals. Nat Immunol 14: 646-653. https://doi. org/10.1038/ni.2604

9. Walker WA (2017) The microbiota in gastrointestinal Pathophysiology, implications for human health, prebiotics, probiotics and dysbiosis. Academic press 227-232. https://doi.org/10.1016 /B978-0-12-804024-9.00025-2

10. Schroeder BO, Bäckhed F (2016) Signals from the gut microbiota to distant organs in physiology and disease. Nat Med 22:1079-1089. https://doi.org/ 10.1038/nm.4185

11. Eckburg PB, Bik EM, Bernstein CN et al (2005) Diversity of the human intestinal microbial flora. Science 308:1635-1638. https://doi.org/10.1126% 2Fscience.1110591

12. Ghoshal UC, Shukla R, Ghoshal U (2017) Small intestinal bacterial overgrowthand irritable bowel syndrome: a bridge between functional organic dichotomy. Gut Liver 11:196-208. https://doi.org/ 10.5009/gnl16126

13. Riordan SM, McIver CJ, Wakefield D, Duncombe VM, Thomas MC, Bolin TD (2001) Small intestinal mucosal immunity and morphometry in luminal overgrowth of indigenous gut flora. Am J Gastroenterol 6:494-500. https://doi.org/10.1111/j.1 572-0241.2001.03533.x

14. Erdogan A, Rao SS, Gulley D, Jacobs C, Lee YY, Badger C (2015) Small intestinal bacterial overgrowth: duodenal aspiration vs glucose breath test. Neurogastroenterol Motil 27:481-489. https://doi.org/10.1111/nmo.12516

15. Alemao CA, Budden KF, Gomez HM, Rehman SF, Marshall JE, Shukla SD, Hansbro PM (2021) Impact of diet and the bacterial microbiome on the mucous barrier and immune disorders. Allergy 76:714-734. https://doi.org/10.1111/all.14548

16. Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA et al (2019) Global regional and national cancer incidence, mortality, years of list lost, years lived with disability and disability adjusted life yraes for 32 cancer groups 1090 to 2015: A systematic analysis of disease study. JAMA Oncol 3:524-548. https://doi.org/10.1001/jamaoncol.2019.2996

17. Geva Zatorsky N, Sefik E, Kya L, Paman L, Tan T G et al (2017) Mining the human gut microbiota for immuno modulatory organisms. Cell 168: 928-943. https://doi.org/10.1016/j.cell.2017.01.022

18. Knight R, Callewaert C, Martoz C, Hyde ERM, Debelius JW et al (2017) The microbiome and human biology. Annu Rev Genom Hum Genet 18:65-86. https://doi.org/10.1146/annurev-genom-083115-022438

19. Huttenhower C, Gevers D, Knight R, Abubucker S, Badger JH, Chinwalla AT, Creasy HH, Earl AM, FitzGerald MG, Fulton RS et al (2012) Structure, function and diversity of the healthy human microbiome. Nature 486:207-214. https://doi.org/10.1038/nature11234

20. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, Nielsen T, Pons N, Levenez F, Yamada T et al (2010) A human gut microbial gene catalogue established by metagenomic sequencing. Nature 464:59-65. https://doi.org/10.1038/nature 08821

21. Chen F, Dai X, Zhou CC, Li KX, Zhang YJ et al (2022) Integrated analysis of the faecal metagenome and serum metabolome reveals the role of gut microbiome-associated metabolites in the detection of colorectal cancer and adenoma. Gut 7: 1315. https://doi.org/10.1136/gutjnl-2020-323476

22. Zhang YJ, Li S, Gan RY, Zhou T, Xu DP, Li HB (2015) Impact of gut bacteria on human health and diseases. Int J Mol Sci 16:7493-7519. https://doi.org/10.3390/ijms16047493

23. Vernocchi P, Gili T, Conte F, Del Chierico F, Conta et al (2020) Network Analysis of Gut Microbiome and Metabolome to Discover Microbiota-Linked Biomarkers in Patients Affected by Non-Small Cell Lung Cancer. Int J Mol Sci 22:8730. https://doi.org/10.3390/ijms21228730

24. Sears CL, Pardoll DM (2011) Perspective: alpha-bugs, their microbial partners, and the link to colon cancer. J Infect Dis 203:306-311. https:// doi.org/10.1093/jinfdis/jiq061

25. Nichols RG, Davenport ER (2021) The relationship between the gut microbiome and host gene expression: a review. Hum Genet 140:47-760. https://doi.org/10.1007/s00439-020-02237-0

26. Haber AL, Biton M, Rogel N, Herbst RH, Shekhar K et al (2017) A single cell survey of the small intestinal epithelium. Nature 551:333-339. https://doi.org/10.1038/nature24489

27. Vivarelli S, Salemi R, Candido S, Falzone L, Santagati M et al (2019) Gut microbiota and cancer: from pathogenesis to therapy. Cancers 1:38. https://doi.org/10.3390/cancers11010038

28. Carbotti M, Scirocco A, Maselli MA, Serveri C (2015) the gut brain axis: interaction between enteric microbiota and central and enteric nervous system. Annu Gatroenterol 28:203-209.

29. Sandrini S, Aldriwesh M, Alruways M, Freestone P (2015) Microbial endocrinology: Host bacteria communication within the gut microbiome. J Endocrinol 225:R21-R34. https://doi.org/10.1530/joe-14-0615

30. Ceranowicz P, Warzecha Z, Dembinski A (2015) Peptidyl hormones of endocrine cell origin in physiological relevance. J Physiol Pharacol 66:11-27.

31. Ravussian Y, Koren O, Spor A, Le Du CC, Gutman R et al (2012) Response of gut microbiota to diet composition and weight loss in lean and obese mice. Obesity 20:738-747. https://doi.org/10.1038%2Foby.2011.111

32. Schmidt TSB, Raes J, Bork P (2018) Human gut microbiome from association to modulation. Cell 72:1198-1215. https://doi.org/10.1016/j.cell.2018.02.044

33. Clarke G, Stilling RM, Kennedy PJ, Stanton C, Cryan JF et al (2014) Minireview: Gut microbiota the neglected endocrine organ. Mol Endocrinol 28:1221-1238. https://doi.org/10.1210/me.2014-1108

34. Louis P, Hold GL, Flint HJ (2014) The gut microbiota, bacterial metabolites and colorectal cancer. Nat Rev Microbiol 12:661-72. https://doi.org/10.1038/nrmicro3344

35. Singh R, Zogg H, Wei L, Bartlett A, Ghoshal UC, Rajender S, Ro S (2021) Gut microbial dysbiosis in the pathogenesis of gastrointestinal dysmotility and metabolic disorders. J Neurogastroenterol Motil 27:19. https://doi.org/10.5056/jnm20149

36. Klampfer L, Einstein A (2003) Inhibition of Interferon γ Signaling by the Short Chain Fatty Acid Butyrate. Mol Cancer Res 1:855–862.

37. Post S E, Ilana L, Brito (2022) Structural insight into protein–protein interactions between intestinal microbiome and host. Curr Opin Struct Biol 74:102354. https://doi.org/10.1016/j.sbi.2022.102354

38. Sivaprakasam S, Prasad DP, Singh N (2016) Benefits of short-chain fatty acids and their receptors in inflammation and carcinogenesis. Pharmacol Ther 164:144-151 https://doi.org/10.1016/j.pharmthera.2016.04.007

39. Bibbo S, Ianiro G, Giambo F, Settanni CR, Commarrota G et al (2022) Role of gut microbiome on immunotherapy efficacy in melanoma. Hum Vaccin Immunother 18:319267569 https://doi.org/10.1080/21645515.2021.1926759

40. Pavonen J, Naud P, Salmeron J, Wheelir CM, Chow SN et al (2009) Efficiency of human Papillomavirus (HPV) against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): Final analysis of a double blind randomised study in young woman. Lancet 374:301-314. https://doi.org/10.1128/CVI.00591-14

41. Matsuo, Taisuke, Yasuyuki (2019) In vitro anticancer activities of B6 vitamers: A mini-review. Anticancer Res 39:7 3429-3432. https://doi.org/10.21873/anticanres.13488

42. Komatsu S, Yanaka N, Matsubara K, Kato N (2003) Antitumor effect of vitamin B6 and its mechanisms. Biochim Biophys Acta Proteins Proteom BBA-PROTEINS PROTEOM 164:127-130. https://doi.org/10.1016/s1570-9639(03)00076-1

43. Dembinsk A, Warzecha Z, Ceranowicz P, Dembiniski M, Cieszkowski J et al (2016) Synergic interaction of a Rifaximin and mutaflor (Escherchia coli Nissel 1917) in the treatment of acetic acid induced colitis in Rats. Gastroenterol Res Pract 312:62-80. https://doi.org/10.1155/2016/3126280

44. Konishi M, Fujiya M, Tanaka M, Uneo N, Moriichi K et al (2016) Probiotic derived ferrichromes inhibits colon cancer progression via JNK mediated apoptosis. Nat Commun 7:12368. https://doi.org/10.1038/ncomms12365

45 Yaghoubi A, Khazaei M, Jalili S, Hasanian SM, Avan A, Soleimanpour S, Cho WC (2020) Bacteria as a double-action sword in cancer. Biochim Biophys Acta - Rev Cancer 1874:188388. https://doi.org/10.1016/j.bbcan.2020.188388

46. Rommasi F (2022) Bacterial-Based Methods for Cancer Treatment: What We Know and Where We

Are. Oncol Ther 10:23–54. https://doi.org/10.1007/s40487-021-00177-x

47. Yaghoubi A, Khazaei M, Hasanian SM, Avan AC, Cho W, Soleimanpour S (2019) Bacteriotherapy in Breast Cancer. Int J Mol Sci 20:5880. https://doi.org/10.3390/ijms20235880

48. Khoshnood S, Fathizadeh H, Neamati F, Negahdari B, Baindara P, Abdullah MA (2022) Bacteria-derived chimeric toxins as potential anticancer agents. Front. Oncol. Sec. Cancer Molecular Targets and Therapeutics 12. | https://doi.org/10.3389/fonc.2022.953678

49. Sheflin AM, Whitney AK, Weir TL (2014) Cancer promoting effects of microbial dysbiosis. Curr Oncol Rep 16:406. https://doi.org/10.1007/s11912-014-0406-0

50. Bell NH, Rebernick JR, Goyert J, Singhal R, Kuljanin M et al (2022) Reuterian in the healthy gut microbiome suppresses colorectal cancer growth through altering redox balance. Cell 40:185-200. https://doi.org/10.1016/j.ccell.2021.12.001

51. Rea D, Coppola G, Palma G, Barberi A, Luciano A (2018) Microbiota effects on cancer: from risk to therapies. Oncotarget 9:17915-17927. https://doi.org/10.18632%2Foncotarget.24681

52. Bhatt AP, Redinbo MR, Bultman SJ (2017) The role of the microbiome in cancer development and therapy. CA Cancer J Clin 67:326-344. https://doi.org/10.3322/caac.21398

53. Geva Zatorsky N, Sefik E, Kya L, Paman L, Tan T G et al (2017) Mining the human gut microbiota for immuno modulatory organisms. Cell 168: 928-943. https://doi.org/10.1016/j.cell.2017.01.022

54. Wroblewski LE, Peek RM JR, Wilson KT (2010) Helicobacter pylori and gastric cancer: factors that modulate disease risk. Clin Microbiol Rev 23(4):713-39. https://doi.org/10.1128/cmr.00011-10

55. Grasso F, Frisan T (2015) Bacterial Genotoxins: merging the DNA damage response in to infection biology. Biomolecules 5:1762-1782. https://doi.org/10.3390/biom5031762

56. Aurther C J, Chanona P E, Muhlbauer M, Tomkovich S, Uronis M J et al (2012) Intestinal inflammation targets cancer-inducing activity of the microbiota. Science 338:120-123. https://doi.org/10.1126/science.1224820

57. Frisan T (2016) Bacterial genotoxins: The long journey to the nucleus of mammalian cells. Biochem Biophys Acta 1858:567-575. https://doi.org/10.1016/j.bbamem.2015.08.016

58. Tejero LM, Galan JE (2000) A bacterial toxin that controls cell cycle progression as a deoxy-ribose nuclease like protein. Science 290:354-357. https://doi.org/10.1126/science.290.5490.354

59. Bergounioux J, Elisee R, Prunier AL, Donnadieu F, Sperandio B et al (2012) Calpain activation by the *Shigella flexneri* effector virA regulates key steps in the formation and line the bacterium epithelial niche. Cell Host Microbe 11:240-252. https://doi.org/10.1016/j.chom.2012.01.013

60. Buti L, Spooner E, Vanderveen AG, Rappuoli R, Covacci A et al (2011) *Helicobacter pylori* cytotoxin associated gene (CagA) subverts the apoptosis stimulating protein of P53 tumor suppressor pathway of the host. Proc Natl Sci USA 108:9238-9243. https://doi.org/10.1073/pnas.1106200108

61. Adachi H, Kamiya T, Hirako M, Misu N, Kobayashi Y et al (2007) Improvement of gastric motility by hemodialysis in patients with chronic renal failure. Smooth Muscle Res 43:179-189. https://doi.org/10.1540/jsmr.43.179

62. Lu R, Wux S, Zhang YG, Xia Y, Liu X et al (2014) Enteic bacterial protein Avr A promotes colonic tumorigenesis and activates colonic beta-catenin signalling pathway. Oncogenesis 3: e105 https://doi.org/10.1038/oncsis.2014.20

63. Ding SZ, Minohara Y, Fan XJ, Wang J, Reyes VE et al (2007) *Helicobacter pylori* infection induces oxidative stress and programmed cell death in human gastric epithelial cells. Infect Immun 75:4030-4039 https://doi.org/10.1128/IAI.00172-07

64. Goodwin AC, Destefano Shields CE, Wu S, Huso DL, Wu X et al (2011) Polyamine catabolism contributes to enterotoxigenic *Bacteroides fragilis* induced colon tumorigenesis. Proc Natl Acad Sci USA108:15354-15359. https://doi.org/10.1073/pnas.1010203108

65. Huycke MM, Moore D, Joyce WM Wise P, Shepard L et al (2001) Extracellular superoxide production by *Enterococcus faecalis* requires demethylmenaquinone and attenuated by functional terminal quional oxidase. Mol Microbiol 42:729-740. https://doi.org/10.1046/j.1365-2958.2001.02638.x

66. Gur C, Ibrahim Y, Isaacson B, Yamin R, Abed J et al (2015) Binding of the Fap2 protein of Fusobacterium nucleatum to human inhitory receptor TIGIT protects tumor from immune cell attack. Immunity 42:344-355. https://doi.org/10.1016/j.immuni.2015.01.010

67. Rossi T, Vergara D, Fanini F, Maffia M, Bravaccini S, Pirini F (2020) Microbiota-Derived Metabolites

in Tumor Progression and Metastasis. Int J Mol Sci 21:5786. https://doi.org/10.3390/ijms21165786

68. Kim J, DeBerardinis RJ (2019) Mechanisms and Implications of Metabolic Heterogeneity in Cancer. Cell Metab 30:434–446. https://doi.org/10.1016/j.cmet.2019.08.013

69. Faubert B, Solmonson A, DeBerardinis RJ (2020) Metabolic reprogramming and cancer progression. Science 368eaaw5473. https://doi.org/10.1126/science.aaw5473

70. Gheorghe AS, Negru SM, Preda M, Mihăilă RI, Komporaly IA, Dumitrescu EA, Lungulescu CV, Kajanto LA, Georgescu B, Radu EA, Stănculeanu DL (2022) Biochemical and Metabolical Pathways Associated with Microbiota-Derived Butyrate in Colorectal Cancer and Omega-3 Fatty Acids Implications: A Narrative Review. Nutrients 14:1152. https://doi.org/10.3390/nu14061152

71. Zeng H, Umar S, Rust B, Lazarova D, Bordonaro M (2019) Secondary Bile Acids and Short Chain Fatty Acids in the Colon: A Focus on Colonic Microbiome, Cell Proliferation, Inflammation, and Cancer. Int J Mol Sci 20:1214. https://doi.org/10.3390/ijms20051214

72. Wang H, Zhao M, Shi F, Zheng S, Xiong L, Zheng L (2023) A review of signal pathway induced by virulent protein CagA of *Helicobacter pylori*. Front Cell Infect Microbiol 13:1062803. https://doi.org/10.3389%2Ffcimb.2023.1062803

73. Wang L, Yi J, Yin XY, Hou JX, Chen J, Xie B, Chen G, Wang QF, Wang LN, Wang XY, Sun J, Huo LM, Che TJ, Wei HL (2022) Vacuolating Cytotoxin A Triggers Mitophagy in *Helicobacter pylori*-Infected Human Gastric Epithelium Cells. Front Oncol 12:881829. https://doi.org/10.3389%2Ffonc.2022.881829

74. Löfmark S, de Klerk N, Aro H (2011) *Neisseria gonorrhoeae* infection induces altered amphiregulin processing and release. PLoS One 6:e16369. https://doi.org/10.1371/journal.pone.0016369

75. Lu R, Bosland M, Xia Y, Zhang Yg, Kato I, Sun J (2017) Presence of Salmonella AvrA in colorectal tumor and its precursor lesions in mouse intestine and human specimens. Oncotarget 8:55104. https://doi.org/10.18632%2Foncotarget.19052

76. Waguia Kontchou C, Gentle IE, Weber A et al (2022) Chlamydia trachomatis inhibits apoptosis in infected cells by targeting the pro-apoptotic proteins Bax and Bak. Cell Death Differ 29:2046–2059. https://doi.org/10.1038/s41418-022-00995-0

77. Martin AL, Calvez TV, Everaert M, Jia R, Sifré E, Seeneevassen L et al (2022) The cytolethal distending toxin modulates cell differentiation and elicits epithelial to mesenchymal transition . bioRxiv 487255. doi: https://doi.org/10.1101/2022.04.06.487255

78. Hajishengallis G, Lamont RJ (2014) Breaking bad: manipulation of the host response by Porphyromonas gingivalis. Eur J Immunol 44:328-38. https://doi.org/10.1002/eji.201344202

79. Ramos-DeSimone N, Hahn-Dantona E, Sipley J, Nagase H, French DL, Quigley JP (1999) Activation of matrix metalloproteinase-9 (MMP-9) via a converging plasmin/stromelysin-1 cascade enhances tumor cell invasion. Journal of Biological Chemistry 74:13066-76. https://doi.org/10.1074/jbc.274.19.13066

80. Garajová I, Balsanom R, Wang H, Leonardi F, Giovannetti E, Deng D, Peters GJ (2021) The role of the microbiome in drug resistance in gastrointestinal cancers. Expert Rev Anticancer Ther 32:165-176 https://doi.org/10.1080/14737140.2021.1844007

81. Stebbing J, Dalgleish A, Gifford-Moore A, Martin A, Gleeson C, Wilson G, Mudan S (2012) An intra-patient placebo-controlled phase I trial to evaluate the safety and tolerability of intradermal IMM-101 in melanoma. Ann Oncol 23:1314-1319. https://doi.org/10.1093/annonc/mdr363

82. Dalgleish AG, Stebbing J, Adamson DJ, Arif S S, Bidoli P, Chang D, Mudan SS (2016) Randomised, open-label, phase II study of gemcitabine with and without IMM-101 for advanced pancreatic cancer. Br J Cancer 115:789-796. https://doi.org/10.1038/bjc.2016.271

83. Daillère R, Vétizou M, Waldschmitt N, Yamazaki T, Isnard C, Poirier-Colame V, Zitvogel L (2016) Enterococcus hirae and Barnesiella intestinihominis facilitate cyclophosphamide-induced therapeutic immunomodulatory effects. Immunity 45:931-943. https://doi.org/10.1016/j.immuni.2016.09.009

84. Iida N, Dzutsev A, Stewart CA, Smith L, Bouladoux N, Weingarten RA, Goldszmid RS (2013) Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. Science 342:967-970. https://doi.org/10.1126/science.1240527

85. Vétizou M, Pitt JM, Daillère R, Lepage P, Waldschmitt N, Flament C, Zitvogel L (2015) Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Science 350:1079-1084. https://doi.org/10.1126/science.aad1329

86. Viaud S, Saccheri F, Mignot G, Yamazaki T, Daillère R, Hannani, D Zitvogel (2013) The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. Science 342:971-976. https://doi.org/10.1126/science.1240537

87. Routy B, Le Chatelier E, Derosa L, Duong C P, Alou M T, Daillère R, Zitvogel L (2018) Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors. Science 359:91-97. https://doi.org/10.1126/science.aan3706

88. Matson V, Fessler J, Bao R, Chongsuwat T, Zha Y, Alegre M L, Gajewski T F (2018) The commensal microbiome is associated with anti–PD-1 efficacy in metastatic melanoma patients. Science 359:104-108. https://doi.org/10.1126/science.aao3290

89. Fessler JL, Gajewski TF (2017) The microbiota: A new variable impacting cancer treatment outcomes. Clin Cancer Res 23:3229-3231. https://doi.org/10.1158/1078-0432.CCR-17-0864

90. McGranahan N, Swanton C (2015) Biological and therapeutic impact of intratumor heterogeneity in cancer evolution. Cancer cell 27:15-26. https://doi.org/10.1016/j.ccell.2014.12.001

91. Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC et al (2018) Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients. Science 359:97-103. https://doi.org/10.1126/science.aan4236

92. Wei W, Sun W, Yu S, Yang Y, Ai (2016) Butyrate production from higher fiber diet protect against lymphoma tumor. Leuk Lymphoma 57:2401-2408. https://doi.org/10.3109/10428194.2016.1144879

93. Zitvogel L, Daillère R, Roberti M et al (2017) Anticancer effects of the microbiome and its products. Nat Rev Microbiol 15:465–478. https://doi.org/10.1038/nrmicro.2017.44

94. Aschtgen SM, Fragkoulis K, Snaz G, Normark S, Selvanova G et al (2022) Enterobacteria impair host P^{53} pathway through mRNA destabilization. Oncogene 41:2173-2186 https://doi.org/10.1038/s41388-022-02238-5

95. Bhang HE, Ruddy DA, Krishnamurthy Radhakrishna V, Caushi JX, Zhao R et al (2015) Studying clonal dynamics in response to cancer therapy using high complexity bar-coding. Nat Med 21: 440-448. https://doi.org/10.1038/nm.3841

96. Dy GK, Adjei AA (2013) Understanding recognizing and managing toxicities of targeted anticancer therapies. CA Cancer J clin 63:249-279. https://doi.org/10.3322/caac.21184

97. Lee J W, Shin JG, Kim EH, Kang HE, Yim IB et al (2004) Immunotherapy and antitumor effectors in vivo by the cytoplasmic fraction of *Lactobacillus casei* and *Bifidobacterium longum*. J vel sci 5:41-48. https://doi.org/10.4142/jvs.2004.5.1.41

98. Nayak RR, Trurnbaugh PJ (2016) Mirror on the wall: which microbes will help heal them all? BMC Med 14:72. https://doi.org/10.1186/s12916-016-0622-6