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Review

Microbiome in cancer: Role in carcinogenesis and impact in therapeutic strategies

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ABSTRACT

Cancer is the world's second-leading cause of death, and the involvement of microbes in a range of diseases, including cancer, is well established. The gut microbiota is known to play an important role in the host's health and physiology. The gut microbiota and its metabolites may activate immunological and cellular pathways that kill invading pathogens and initiate a cancer-fighting immune response. Cancer is a multiplex illness, characterized by the persistence of several genetic and physiological anomalies in malignant tissue, complicating disease therapy and control. Humans have coevolved with a complex bacterial, fungal, and viral microbiome over millions of years. Specific long-known epidemiological links between certain bacteria and cancer have recently been grasped at the molecular level. Similarly, advances in next-generation sequencing technology have enabled detailed research of microbiomes, such as the human gut microbiome, allowing for the finding of taxonomic and metabolomic linkages between the microbiome and cancer. These investigations have found causative pathways for both microorganisms within tumors and bacteria in various host habitats far from tumors using direct and immunological procedures. Anticancer diagnostic and therapeutic solutions could be developed using this review to tackle the threat of anti-cancer medication resistance as well through the wide-ranging involvement of the microbiota in regulating host metabolic and immunological homeostasis. We reviewed the significance of gut microbiota in cancer initiation as well as cancer prevention. We look at certain microorganisms that may play a role in the development of cancer. Several bacteria with probiotic qualities may be employed as bio-therapeutic agents to re-establish the microbial population and trigger a strong immune response to remove malignancies, and further study into this should be conducted.

1. Introduction

With trillions of commensal bacteria, the mammalian gut is arguably one of the most advanced communities of commensal bacteria. Microorganisms found in the gut include archaea, bacteria, protists, fungi, and viruses, with bacteria being the most abundant [1]. The microbiota can affect human health by producing key metabolites, metabolizing nutrients, and producing toxins that block pathogenic invaders, restrict their growth, produce beneficial microbial products, and metabolize the nutrients and poisons of invading species [2,3]. A multitude of functions are regulated by the interaction of the gut microbiota with stromal and epithelial cells. These functions include pathogen invasion and infection, pathogen overgrowth management, host-microbiota symbiosis and mucosal immunological homeostasis, regulating metabolism, and acting as a barrier [4–9].

Bacteria, fungi, and viruses can be found on epidermal surfaces [10], the nares, the respiratory tree [11,12], the ductal system of exocrine organs such as the breast [13], the vagina [14], and the gastrointestinal (GI) tract [15–17]. Bacteria routinely cross the GI mucosa and are exposed to the enterohepatic circulation [18]; and evidence suggests that some bacteria may concentrate in tumors due to aberrant tumor vasculature, allowing for residency and extravasation. The metabolic

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and population responses of microbiota to changes in their microenvironment are becoming better understood thanks to an avalanche of next-generation sequencing studies that can now identify and quantify the species present in each of these microbiotas without the bias that traditional bacterial culture methods introduce. The focus of this review will be on the links between the gut microbiome and cancer, but it will also consider the microbiome of tumors. With the introduction of high-resolution next-generation sequencing of bacterial 16S ribosomal RNA, researchers can now identify and quantify a huge number of species in the gut microbiome. With this knowledge, it was discovered that the majority of species were not routinely culturable, prompting the development of far more culture techniques over the last decade [19,20], with a special focus on anaerobes, which make up the majority of a typical microbiome but are only a minority of organisms routinely cultured. With the development of high-throughput sequencing, improved sequence assembly techniques, and far more comprehensive databases of sequenced organisms [21,22], high-depth metagenomic sequencing has gained traction [23], allowing for the identification and quantification of organisms from a mixed metagenomic sample, such as stool or a mucosal biopsy, down to individual bacteria [24,25]. These investigations' major findings are astonishing. The average human gut microbiome has 1013–1014 organisms, the same number as human cells [26], as well as a unique genome with up to 3 106 genes, significantly more than the human genome. Most gut microbiomes studied so far have evolved in conjunction with their hosts over millions of years (with a few notable exceptions [27]).

The bacterial microbiome has metabolic pathways that are not found in the host DNA. The microbiome of the host is maintained and developed by the host's diet, which is regulated by the immune system and epithelial interactions to suit the host's nutritional demands. Four phyla of bacteria dominate the human gut microbiome. *Firmicutes* and *Bacteroidetes* account for approximately 90% of the total, while *Proteobacteria* and *Actinomycetes* are less abundant [28]. *Firmicutes* are Gram-positive bacteria such as anaerobic *clostridia, streptococci,* and *enterococci*. Bacteroidetes, such as Bacteroides the *taiotamicron* and *Bacteroides fragilis*, are Gram-negative rods that can break down complex polysaccharides. *Bifidobacteria*, commonly referred to as probiotic bacteria, are Gram-positive bacteria with a high GC content that belong to the Actinobacteria family. Gamma proteobacteria, Escherichia coli, and Klebsiella species are all members of the Proteobacteria family of Gram-negative bacteria. Researchers attempted to characterize individuals based on the major constituents of their gut microbiome in the early 2010 s, leading to the idea that different humans have different "enterotypes," which are influenced by diet and geography [29], but also intrinsic to the individual in some ways, owing to founder effects of the initial colonizing organisms and the individual immune system. Most microbiome differences, according to further data, occur along a continuum of the ratio of two genera in the phylum *Bacteroidetes, Prevotella* and *Bacteriodes*, with the latter being more common in those who eat a plant-rich diet high in complex polysaccharides [30].

Despite the fact that the individual human microbiome appears to be rather resilient, antibiotic therapy can cause serious harm [19]. It's also worth mentioning that the consequences of making deliberate dietary changes have received very little consideration. Certainly, organisms protected in crypts inside the epithelial mucous layer can repopulate a significant portion of the microbiome [28], and interactions between less abundant species may be important for preserving the overall structure of the individual microbiome [31]. Researchers found a variety of results depending on the group analyzed, but one clear trend is that bacteria associated with a plant-based diet are connected to a lower risk of colon cancer. Short-chain fatty acids such as acetate, propionate, and butyrate are produced by the microbiota and have been shown to be anti-inflammatory in colonic tissues by triggering T-regulatory cells [32].

We're learning more about immunological interactions that occurs across epithelial surfaces as we gain a better grasp of the microbiome's components. Bacteria, bacterial phages, and fungi train both the innate and adaptive immune systems from across the epithelial surface, via direct antigen-presenting cell interactions and metabolite regulation of host signaling, particularly short-chain fatty acids like butyrate [33]. Some animals may create chemicals that bind to human receptors directly [34]. The host uses antimicrobial peptides [35], inactivated IgA [36,37], and metabolic substrates like mucin proteoglycans to keep or reject certain species [33,38,39].

Tumor tissue is full with microbes, including bacteria, fungus, viruses, and mycoplasmas. On the inside of cancerous and tumor-infiltrating immune cells, researchers have found traces of microbial residues such DNA and RNA, peptides, and cell wall components. Fatty acids and inosine, among other microbial metabolites, can build up inside tumors and bind to receptors on both cancerous and immune cells. Gram-positive bacteria create membrane vesicles derived from microbes that include a variety of microbial proteins, nucleic acids, and peptidoglycan. However, it has yet to be proven that they exist within the tumor. They all play a role in tumor development, progression, metastasis, and immunological responses [40].

The role of the tumor microbe microenvironment in the tumor immune microenvironment is multifaceted: either as an immune activator, inhibitor, or bystander. The underlying mechanisms include: (I) the presentation of microbial antigens by cancer cells and immune cells, (II) microbial antigens mimicry shared with tumor antigens, (III) microbe-induced immunogenic cell death, (IV) microbial adjuvanticity mediated by pattern recognition receptors, (V) microbe-derived metabolites, and (VI) microbial stimulation of inhibitory checkpoints. The tumor microbe microenvironment modulates the tumor immune microenvironment, making it a potential target for improving immunotherapy. It is a novel field facing major challenges and deserves further exploration [40].

We explore the role of the bacterial microbiome in the interaction between cancer and the immune system, as well as the therapeutic possibility of directly modifying the commensal microbiota to improve cancer immunotherapy efficacy. The association between the gut microbiome and cancer is discussed in this article. Furthermore, we discuss the potential pathways employed by the gut microbiota to influence the immune system in a bilateral manner, which could contribute to cancer formation and could be used as prospective cancer treatment and prevention measures.

2. Associative studies of the microbiome and cancer

Microbial-driven tumors are thought to account about 20% of all tumors worldwide [41]. The previous epidemiological observations have been augmented by extremely sensitive technologies for investigating the microbiome more thoroughly in tissues thanks to contemporary sequencing approaches. Several investigations employing metagenomic approaches discovered novel pathogens that were enriched in a variety of cancer forms when compared to either juxtatumoural tissue or healthy patient tissues. Microbial DNA signatures were found in tumors that arose in places that were previously thought to be sterile. The definition of a tumor-specific colonic [42] and laryngeal [43] microbiome has progressed. Many of these associative investigations left unanswered the question of whether the organisms discovered a hospitable tumor niche as a bystander, or whether the bacteria contributed to the tumor's pathogenesis or persistence. Certain studies of the metagenome and bacteria associated with malignancies have caused dispute due to the technological complexity of the investigations. Different representations of the gut microbiome in feces vs biopsy samples, problems correctly assigning genes in metagenome studies, and challenges recognizing the source of microbial genes in sequencing material from paraffin blocks are just a few instances [44].

Furthermore, due to the low bacterial biomass in tumor samples, utilizing DNA extraction kits to separate signal from background contamination may be problematic. Because numerous laboratories

sequence samples using a range of methodologies for sample extraction, processing, and data analysis, the experimental details that are chosen can affect the results [45]. In one study, the 'kitome' from different lots of DNA extraction kits was found to account for the majority of the variance in a collection of samples analyzed using metagenomics sequencing [46]. The need of repeating results across different research and laboratories is crucial for developing trust in these findings, and efforts to standardize and confirm optimal sequencing processes across the field will almost certainly continue. Despite the field's infancy, it appears clear that a variety of organisms can be found in both metastatic and primary cancer sites, possibly as a result of haematogenous [47] and local spread from a variety of sources, including the oral plaque microbiome [48] and that these organisms may contribute to tumour inflammation.

3. Modulation of cancer behaviour by microbiome transfer and removal

Microbial manipulation as a strong immunotherapeutic method has been sparked by the correlations between certain gastrointestinal bacteria and the activity of systemic lymphoid tissues. Preliminary studies [49,50] show that if intratumoral microbiota are found to be abundant and immunologically active in most patients, such therapies must take into account the microbial niches and their cross-talk (Fig. 1). Because it contains the greatest number of microorganisms in the mammalian body, the colon has long been the primary site for researching carcinogenesis in experimental mice. In a Cdx2-inducible adenomatous polyposis coli (APC) null mouse model of colon cancer, in which mice develop cancer in the distal colon similar to the human condition caused by loss of APC, as well as showing an inflammatory interleukin (IL)−23/IL-17 signature, the mouse gut microbiome had a major influence on tumorigenesis via inflammation modulation [51].

Antibiotics reduced tumor burden just as much as removing the IL-23

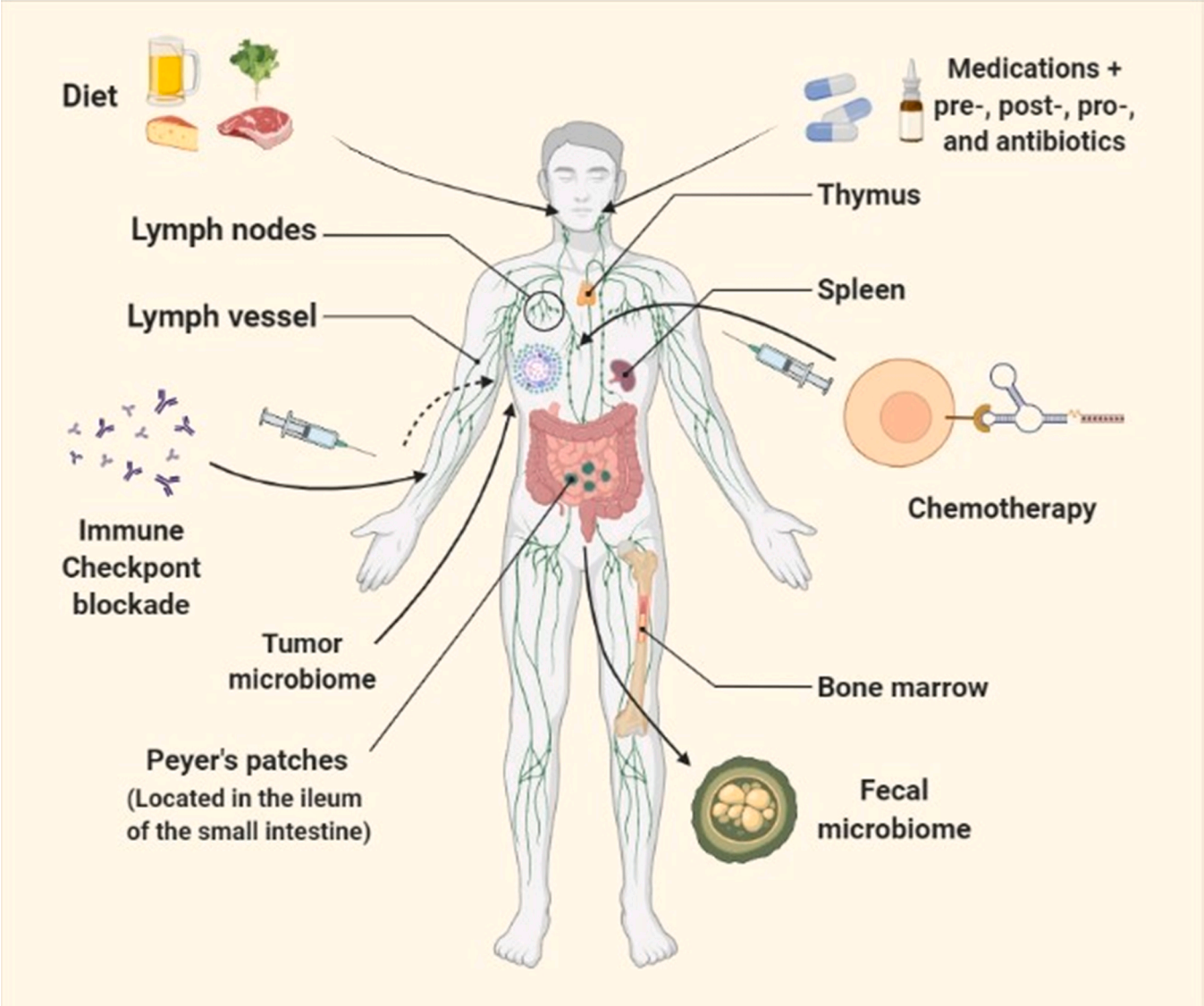

Fig. 1. Factors to consider when modifying the internal cancer microbiota. Gut and tumor microbiomes can be altered by a variety of factors, including diet, medicine, and prebiotics, postbiotics, probiotics, and antibiotics. One way or the other, these microbiomes and cancer treatments may have an impact on one another (chemotherapy and immunotherapy). As a result of chemotherapy, gut microbiome composition alterations may boost treatment efficacy [57]; in other situations, bacteria may destroy medication [58]. It may be helpful for one treatment technique, but detrimental for another, to alter the microbiome of the gut or tumor. In the literature, dotted arrows indicate areas where there are gaps [59].

receptor. To activate the innate immune system, TLR 2 and MYD88 signals were employed. Zackular et al. [52] used an azoxymethane (AOM)/dextran sulphate sodium (DSS) tumor model to show that the microbiota of tumor-bearing mice increased the incidence and severity of colorectal malignancies when transmitted to germ-free recipients more than the microbiota of non-tumor-bearing AOM/DSS mice. The microbiome's causative potential in increasing colorectal tumor growth by causing inflammation was further highlighted. Some malignancies appear to be critically reliant on their resident microbiota to survive and evade the immune system when patients are given antibiotics, while some cancers appear to be critically reliant on their microbiota to survive and evade the immune system when patients are given antibiotics. The most well-known example is the treatment of *Helicobacter pylori* induced stomach mucosa-associated lymphoid tissue (MALT) lymphoma with lansoprazole 30 mg, amoxicillin 1 g, and clarithromycin 500 mg (PREVPAC) [53]. In 39 of 44 individuals with ocular adnexal lymphoma, Chlamydophilapsittaci infection was revealed to be the etiology [41,42]. Doxycycline treatment resulted in six full remissions and 16 partial remissions in 34 patients [54,55]. As expected, chlamydia reduction and eradication levels were linked to tumor regression. In a small research with pseudomyxomaperitonei, PREVPAC combined with standard hyperthermicmitomycin C intraperitoneal chemotherapy with tumor debulking improved treatment outcomes [56].

4. Metagenomic human studies identifying microbiota associated with cancer tissues

Many bacteria are significant human symbiotes. They establish distinct microbiota communities, participate in a variety of biological processes in their hosts, and hence have a significant impact on human health [60]. Metagenomic sequencing has become popular in human microbiota research due to its ability to examine all genetic elements in an environment as a whole without the necessity for microorganism isolation or cultivation. Human metagenomic research identifies microbiome linked to cancer tissues (Table 1) [61]. Several long recognized epidemiological associations between particular bacteria and cancer are now understood at the molecular level. At the same time, the arrival of next-generation sequencing technology has permitted a thorough exploration of microbiomes such as that of the human gut, enabling observation of taxonomic and metabolomic relationships between the microbiome and cancer [38]. Meanwhile, interest in the possible relationships between microorganisms and the different stages of cancer development has been rising and numerous mechanisms by which bacteria and yeast may initiate or promote carcinogenesis are currently under investigation. In particular, a persuasive body of evidence suggests a possible etiological role involving the metabolism and production of carcinogenic products, such as acetaldehyde. Other suggested mechanisms include the induction of chronic inflammation and direct interference with eukaryotic cell cycle and signaling pathways [61].

Table 1
Metagenomic human studies identifying microbiota associated with cancer tissues.

Type of tissue	Between-species distinction	References
Breast cancer	*Streptococcus, Prevotella*, and Veillonella species were found in higher numbers in cancer tissues.	[62,63]
Oesophageal cancer	Species of *Streptococcus, Prevotella,* and Veillonella were found in higher numbers in cancer tissues.	[64–66]
Head and neck cancer	The amount of *Fusobacterium, Prevotella*, and *Gemella* species in cancer tissues rose.Cancer tissues had decreased levels of Streptococcus and Rothia species.	[43]
Prostate cancer	*Propionobacterium acnes* was found at higher numbers in cancer tissues.	[67–69]
Pancreatic cancer	*Enterobacteriaceae, Pseudomonadaceae, Moraxellaceae*, and *Enterococcaceae* were found in abundance in pancreatic cancer tissues.	[58]
Colorectal cancer	Colorectal cancer is a type of cancer that affects the colon. In cancer tissues, the number of *Fusobacterium, Selenomonas,* and *Leptotrichia* species increased.	[70–72]

Table 2
Types of cancer development and carcinogenesis processes mediated by various microbiota.

Cancer	Bacteria that cause cancer	Mechanisms of carcinogenesis	Reference
Gallbladder cancer	*Salmonella typhi*	cytolethal distending toxin B (CdtB); biliary deoxycholate; cholic acid derivatives; p53 gene mutations; protein kinase activation; cytolethal distending toxin B (CdtB); biliary deoxycholate; Upregulation of the PI3K pathway; 5-alpha,6-alpha-epoxide cholesterol	[73–75]
Lung cancer	*Chlamydia pneumoniae*	Increased secretion of cytokines, IL-8, IL-10, and TNF; overexpression of miRNA-328; activation of lung-resident T cells; synthesis of Myd88-dependent IL-1b and IL-23; production of reactive oxygen species; increased secretion of cytokines, IL-8, IL-10, and TNF	[76–78]
Colorectal cancer	*Streptococcus bovis, Helicobacterpylori, Bacteroidesfragilis, Enterococcusfaecalis, Clostridiumsepticum, Fusobacterium spp.,* and *Escherichia coli*	Bacteroidesfragilis toxin secretion; activation ofNF-B; expression of IL-17A and TNF-;-catenin; stimulation of IL-17R, NF-B, and Stat3 signals; induction of colibactin (clbB) and Bacteroidesfragilis toxin (BFT) gene expression; colonic epithelial DNA damage	[79–81]
Breast cancer	*Methylobacteriumradiotolerans, Sphingomonasyanoikuyae*	The microbiota secretes bioactive metabolites such as estrogens, short-chain fatty acids, amino acid metabolites, or secondary bile acids; dysbiosis	[82–84]
Bladder cancer	*Staphylococcus albushemolytic, Staphylococcusaureus, Klebsiellaspp., Proteus mirabilis, and E. coli*	DNA methylation; N-nitrosamine synthesis; reactive chemical species	[85,86]

5. Mechanisms of carcinogenic microbes

There are some microbes that induce cancer (Table 2). Some microbiota includes *Salmonella typhi, Chlamydia pneumoniae, treptococcusbovis, Helicobacterpylori, Bacteroidesfragilis, Enterococcusfaecalis, Clostridiumsepticum, Fusobacterium spp., and Escherichia coli, Methylobacterium radiotolerans, Sphingomona syanoikuyae, taphylococcusalbushemolytic, Staphylococcusaureus, Klebsiellaspp., Proteus mirabilis,* and *E. Coli* are causes of cancer.

6. Mechanistic studies of key carcinogenic organisms

Several components of human virology, such as the *human papillomavirus* (HPV) and the *hepatitis B* virus, are prominent carcinogenic pathogens that will not be treated here. The bacteria *H. pylori* and *Fusobacterium nucleatum* are the most commonly associated to cancer [87]. Increased host cell turnover, genotoxic chemical production, protumourigenic inflammation and nuclear factor-B (NF-B) activation, as well as downregulation of natural killer (NK) and T-cell-mediated immune surveillance [88].

6.1. Genotoxic and non-genotoxic bacterial toxins

Certain bacteria have been found to create genotoxic compounds and other cancer-causing poisons. Enterotoxic *Escherichia coli* strains containing the pks gene cluster produce calobactin, a polyketide that promotes double-strand breaks in mammalian cell DNA [89]. When *E. coli* with the pks gene is administered to IL-10 mutant mice, the number of tumors increases. Other inflammatory bacteria, such as *Enterococcus faecalis* or *E. coli* without pks, cause inflammation but not cancer. As a result, the effects of inflammation were separated from those of an E. coli-borne genotoxin in this animal. In the metagenome of mucosa-associated colon tissue specimens, the toxigeneicpks gene cluster was found in 14 of 21 CRC patients and only five of 24 healthy controls, implying that this microbial gene cluster and CRC are intimately related [90]. Enterotoxin-containing *B. fragilis*, on the other hand, promoted cancer in the APCmin/+ mice via an inflammation-dependent mechanism. Stat3 activation was required to activate Th17 phenotypes. As a result, bacteria may enhance inflammation, giving certain genotoxins to speed up the process or raising the overall risk of carcinogenesis [91].

6.2. Fusobacterium causes inflammation, proliferation, and loss of immune surveillance

Multiple laboratories have found increases in Fusobacterium species in CRC samples compared to healthy or precancerous inflamed colon tissues [42,71,92]. The findings are trustworthy since they originate from a wide range of geographic regions, age groups, sequencing cores, and computational approaches, all of which point to the same conclusion. Using culture and metagenomic sequencing, Fusobacterium 48 was discovered in colorectal liver metastases, demonstrating that colorectal tumor cells provide a unique environment for Fusobacterium. Fusobacterium was investigated as a probable cause of CRC based on these findings, which were primarily associative [70].

F. nucleatum isolates increased carcinogenesis in the APCmin/+ CRC model when administered orally, but not in inflammation-only models such as IL-10 deletion mice or Tbet/Rag2 deletion mice. This reveals that generating inflammation by Fusobacterium increased carcinogenesis in a tumor-prone animal, but that as inflammation worsened, tumorigenesis accelerated [71].

In the microenvironment of Fusobacterium-induced cancers, there are more myeloid-derived suppressor cells (MDSCs). MDSCs have been demonstrated to change patient prognosis and promote tumor growth [93], at least in part by impeding immune surveillance. According to in vitro mechanistic studies [94]. TIGIT can also be linked by Fusobacterium's Fap2 adhesin protein. TIGIT, a tumor-killing activating checkpoint protein on natural killer cells (NK cells), is being investigated as a possible immunotherapy target [95]. The functional suppression of this anti-tumour NK activity by Fusobacterium binding to TIGIT suggests a viable approach for tumors to avoid immune destruction [94]. Fusobacterium has a unique ability to become an invasive infection that can live inside cells, allowing it to avoid immune detection even further. The Fusobacterium FadA surface protein binds to E-cadherin on epithelial cells, allowing for cellular absorption and invasion of the host cell. In vitro, the inflammatory cytokines IL-6, IL-8, and IL-18 are released by the epithelial cancer cell line HCT116 as a result of this interaction. Because clathrin inhibitors blocked FadA-mediated absorption of Fusobacterium and non-invasive Fusobacterium lacking FadA did not produce cytokines, the inflammatory effects were predominantly due to Fusobacterium invasion into the host epithelium [96].

Fusobacterium may play a function in carcinogenesis even if the immune system isn't involved. Binding to E-cadherin promotes proliferative -catenin signaling, which may lead to cancer. The intracellular habitat of Fusobacterium is also expanded [96].

In a separate investigation, Fusobacterium culture-positive tumors and quantitative polymerase chain reaction Fusobacterium-negative human malignancies were used to construct patient-derived xenograft models (both primary and hepatic metastases). Only Fusobacterium-positive tumors were able to engraft, according to the researchers. Tumours passed down four generations had kept their qualities. The microbial species survived four generations in malignancies. The When these tumors were treated with metronidazole in vivo, the amount of Fusobacterium in them was drastically reduced, as were tumor proliferation rates. According to these findings, Fusobacterium may have a function in tumor growth that is immune-independent [70]. When you consider that Fusobacterium moves to metastatic areas with tumor cells, you can see why a symbiotic interaction between the organism and Fusobacterium-associated cancer is necessary [97,98].

Fusobacterium carriage in tumor tissue has been linked to greater levels of NF-B transcripts [71,96], lower CD3-positive T-cell loads, and a worse prognosis, suggesting that this microorganism is associated with malignancies that lack antitumor immune cell activity. Bacteroides, Selenomonas, and Leptotrichia appear to live in similar environments to Fusobacterium [70,72].

6.3. Propionobacterium and tumourigenesis in the prostate

Bacterial tumorigenesis appears to be ubiquitous, not just in the gut. Using culture techniques, fluorescence microscopy, and nucleic acid detection, Propionobacterium acnes has been found as a component of prostate cancer in various studies [68,69]. Surprisingly, the surface features of these *P. acnes* strains differed significantly from those of *P. acnes* strains isolated from skin samples. These tumor-associated bacteria were also capable of infecting and penetrating host cells, as well as triggering COX-2 signaling, which aided cell growth in vitro. *P. acnes* from prostate cancer patients was administered to mice's prostates in vivo, causing enhanced inflammation and cell proliferation [99].

6.4. Distal oncogenic effects of bacteria

The gut microbiota shows that to influence tumorigenesis in addition to the GI and mucosal membranes. The liver and the intestines are linked physiologically through the portal circulation and alter in the GI microbiota that frequently affect the liver [100].

In mice subjected to a single dose of diethyl nitrosamine and repeated doses of the hepatotoxin carbon tetrachloride, carcinogenesis was reduced by partially ablation of the gut microbiota with antibiotics in an inflammatory and fibrotic model of hepatocellular carcinoma (HCC). Late in the sickness model's course, when fibrosis had already established, antibiotic therapy was still effective, suggesting that liver

fibrosis and inflammation did not produce HCC on their own. Mice with entire TLR4 knockouts or liver-specific knockouts exhibited fewer tumors and smaller tumors in the model, indicating that TLR4 activation in resident liver cells is essential for oncogenesis. Lipopolysaccharide, which is produced by bacteria, is TLR4's major ligand (LPS). The oncogenic effect of the microbiota in a TLR4 knockout host was not restored by TLR4 wild-type bone marrow, showing that the microbiota's oncogenic effect is mediated by resident cells in the liver. When taken together, our findings imply that LPS produced by the microbiota, which is the primary ligand for TLR4 activation, promotes carcinogenesis [100].

Another study discovered that the microbiota's influence on host bile acids is a carcinogenic driver. The liver produces primary bile acids, which are subsequently released into the small intestine, where bacteria convert them into deconjugated, secondary, and tertiary bile acid moieties, which are then reabsorbed and returned to the liver via the portal circulation [62]. DCA, a secondary bile acid product, is highly carcinogenic and induces DNA damage in hepatocytes [101,102]. DCA also causes senescence in hepatic stellate cells, which leads to an inflammatory response in the liver. High-fat diets promote the growth of Clostridium XI and XIV clusters that alter bile to create more DCA. Nonalcoholic steatohepatitis advanced to HCC when a high-fat diet was combined with a microbiome rich in bile acid-modifying clostridia. Because Clostridia are vancomycin-sensitive, tumorigenesis was prevented by employing a combination of antibiotics or vancomycin alone. Even when antibiotics were present, injecting DCA resumed carcinogenesis, proving that the carcinogen in the system is bacterially generated DCA. Inflammatory signals like IL-6 and IL-1 were also produced by the microbiome [62]. Although oesophageal cancer is less strongly connected to Clostridium species, it is likely caused by comparable mechanisms [101].

So far, we've looked at the roles of different species and Cancer-causing and cancer-promoting substances in the microbiome. Several microbiome constituents, on the other hand, can interact with the immune system to help the body fight cancer in specific situations. Microbial-based immunotherapy began in the late 1800 s with anecdotal reports of cancer cures following serious infections, followed by the use of Coley's toxins in sarcomas in the late 1800 s [103] and, from the 1970 s to the present, the use of Bacillus Calmette–Guérin (BCG) as a topical intravesical therapy for bladder cancer [104].

In the last decade, the use of checkpoint inhibitors in immunotherapy has revealed a crucial role for the microbiome in modulating the anticancer immune microenvironment.

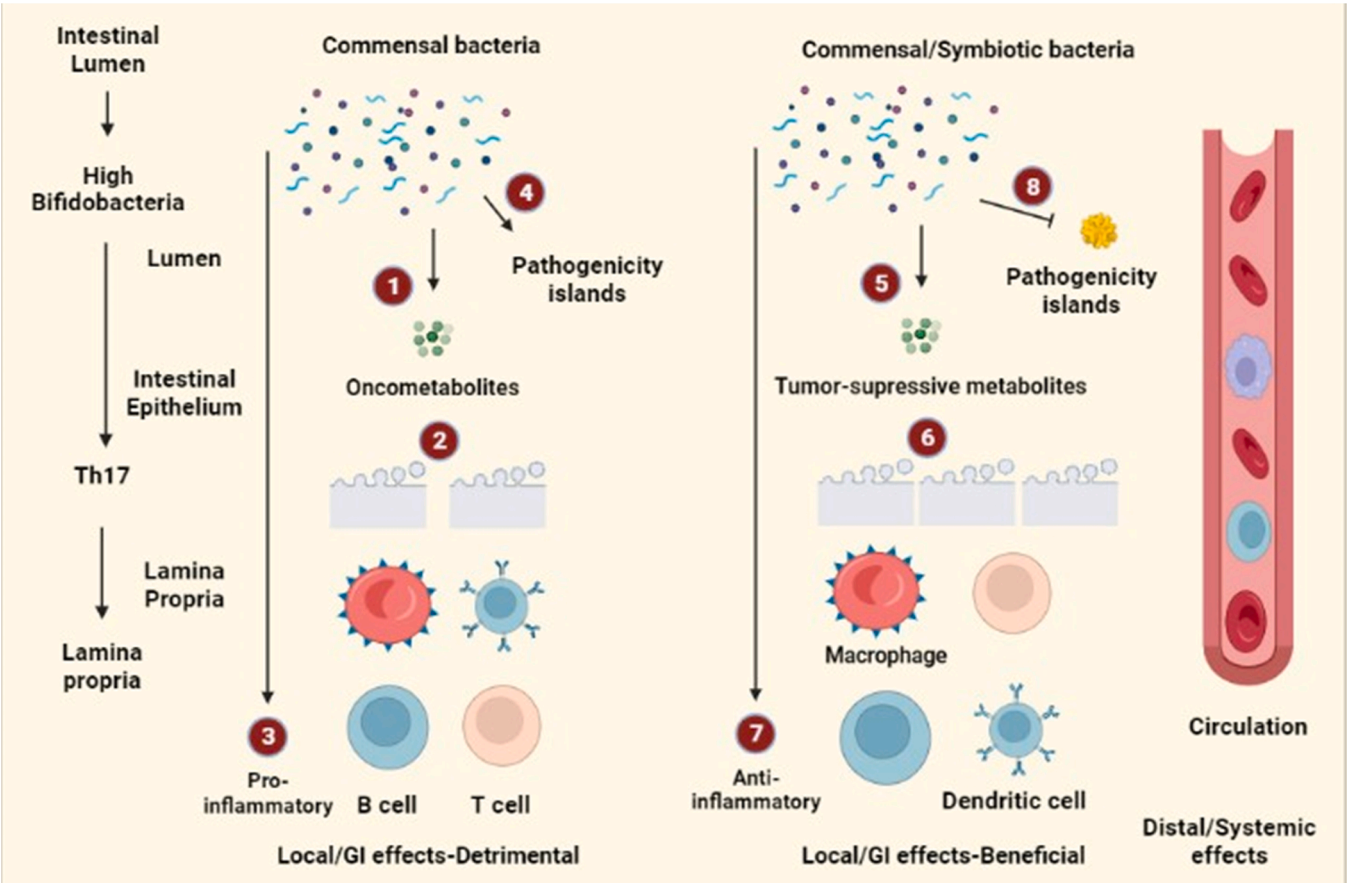

Fig. 2. The gut microbiome influences tumorigenesis differentially in the GI tract and at distant locations. Under a single layer of intestinal epithelial cells that separates the lumen from commensal microbes, immune cells (4 unique colours) the lamina propria beneath it are displayed. Oncogenic (Left box) or tumor suppressive effects of the bacteria might be localized (Center box) or distal (Right box) in nature, mediated through the circulation Gut microbiota may have a variety of broad impacts on tumorigenesis, including (Left box): 1) production of putative oncometabolites, such as hydrogen sulfide; 2) impairment of barrier function, that enhances immune cell sensitivity to bacterial endotoxins (e.g., lipopolysaccharides) and antigens; and 3) immediate impacts of bacterial metabolites and antigens on immune cells to stimulate inflammation by shifting immune cell elements (e.g., the impact of fragmented bacterial populations on T-helper 17 [TH17] cells) (Center box) 5) the manufacturing of putative tumor-suppressive metabolites, such as butyrate, which function through multiple mechanisms; 6) barrier function; 7) immediate impacts on immune cells to protect inflammatory responses by shifting immune cell subsets (e.g., butyrate's ability to stimulate regulatory T-cells) and dampening the immune cell sensitivity through the use of immunoregulatory cytokines (e.g., IL-10); and 8) competitive exclusion of pathogenic bacteria, similar to the prevention Right-hand box: Gut microbiota may have oncogenic or tumor-suppressive effects at distant locations in the body via the circulation of microbiota, microbial metabolites, activated or suppressed immune cells, and cytokines [105].

7. Microbial mechanisms of oncogenesis and tumor suppression

Bacteria in our bodies influence the development of cancer by influencing our immune systems and causing inflammation. So, it is not unusual that the gastrointestinal system gets a lot of attention. Most commensal bacteria are located in the gastrointestinal system, which is also the major area of digestion and nutrient absorption. Other mucosal and lymphoid tissues do not contain as many immune cells as the gastrointestinal system. A number of microbially mediated mechanisms, as seen in Figs. 2 and 3 and described in the next subsections, can aid or hinder tumorigenesis.

7.1. Immune system and inflammation

Inflammation and cancer have a close connection in CRC. Aspirin and other nonsteroidal anti-inflammatory medicines (NSAIDs) have a greater protective effect against colon cancer than other cancers [106–108]. A preclinical investigation on mouse models found a relationship between inflammation and colorectal cancer (CRC) in the gut microbiota. Colitis develops in the IL-10 mutant mice when they receive fecal microbiota from pathogen-free animals, even when they are maintained in a germ-free environment [109]. IL-10 is an immunosuppressive cytokine, according to this study, and it lowers immune responses in response to common gut bacteria. In contrast to wild-type mice, IL-10 mutant mice with conventional microbiota have an inflammatory phenotype that promotes colonic tumor penetrance and multiplicity in response to AOM treatment [110]. To test this hypothesis, we used an IL-10-mutant mouse that had been infected with a strain of Bacteroides vulgatus that was moderately colitogenic. NF-B, a mechanism essential for controlling the innate immune response, is associated with inflammation generated by the microbiota and colorectal cancer. Endotoxins (e.g., lipopolysaccharides, flagellin) are also recognized by TLRs, which activate an inflammatory response through the MyD88 adaptor and the NF-B transcription factors. The MyD88 knockout prevents colonic cancers in AOM-treated, IL-10 knockout mice housed in a pathogen-free environment with microbiota [110].

We must distinguish between tumor-suppressing local immune responses that are specific to the tumor microenvironment and long-term inflammation that may be associated with tumor growth. Th17 cells are dependent on microbiota since germ-free animals lack them and they are triggered by particular microbiota subsets, such as segmented filamentous bacteria, in the gastrointestinal tract [111]. Some tumors can be infiltrated and eradicated by TH17 cells, but data suggests that they may also be associated with a poorer prognosis in other cancer patients [112]. Enterotoxigenic *Bacteroides fragilis* (ETBF) encodes a pathogenic toxin that can trigger TH_{17}-mediated colitis, with concurrent colon-specific signal transducer and activator of transcription 3 (STAT3) activation and tumor induction in susceptible Apc^{Min} (adenomatous polyposis coli [Apc] multiple intestinal neoplasia) mice, which is reversed by IL-17 antibody blockade [91].

Microbe-produced butyrate has been demonstrated to transform naive T and dendritic cells into TReg cells [32,113,114]. Although butyrate-mediated HDAC inhibition is capable of activating FOXP3 epigenetically, activation via G protein-coupled receptors (GPRs) such

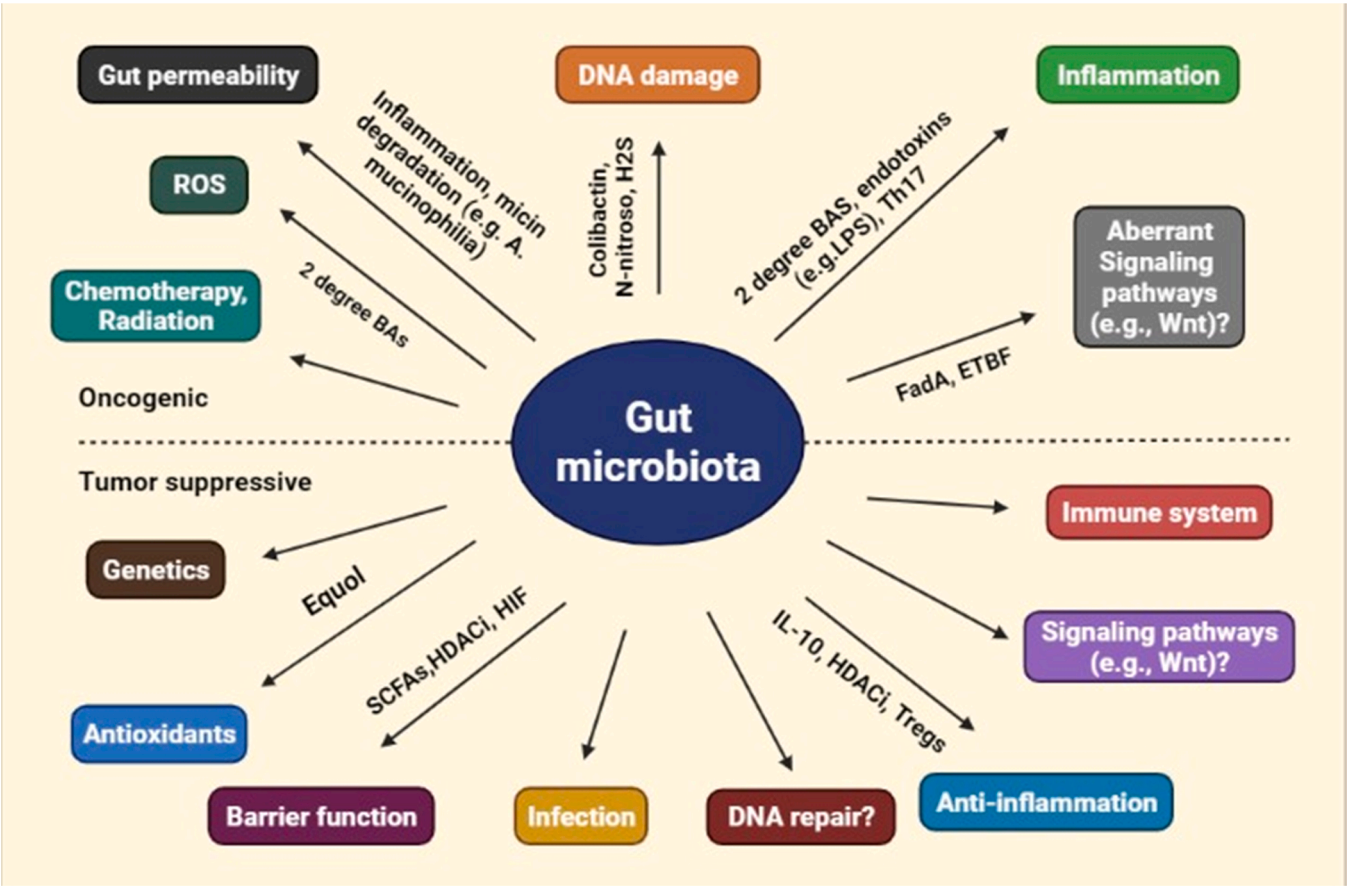

Fig. 3. Oncogenesis and tumor suppression mediated by microorganisms. Each of the biological processes indicated at the end of each line is a way that microbiota can promote oncogenesis or tumor suppression. A symmetrical arrangement of the processes is used to illustrate the fact that many of them are in direct opposition to one another. It's possible to see a variety of microorganism gene products, metabolites and immune modulators along the arrows of the diagrams. Further details are provided in the text. To indicate systems that have yet to be fully explained, the question marks are used. E. coli, Enterobacteriaceae, Fusobacterium adhesion A (FadA), HDAC, Interleukin (IL), and lipopolysaccharides (LPS) are all examples of bacteria that can cause disease (LPS) [105].

as GPR43 and 109a can lead to an increase in the number of TRegulatory cells. In cancer, the role of TReg cells is not clear cut. If TReg cells are infiltrated into the tumor microenvironment, they may hinder anti-cancer responses [115].

Immune cell responses are influenced indirectly by changes in gut barrier function due to the influence of intestinal microbiota on gut barrier function. Bacteria in the lumen are separated from intraepithelial lymphocytes and innate and adaptive immune system cells by an epithelial layer of just one cell. A 100 μm-thick mucus layer produced by goblet cells shields the colonic epithelium, preventing most germs from coming into direct contact with and passing through this protective barrier. Unlike other T cells, intraepithelial lymphocytes produce proinflammatory cytokines in response to antigens without the need for priming. A mouse model's mucus and barrier function can be maintained by diet and gut microbiota [116]. There was a drop in fiber-fermenting bacteria, particularly butyrate-producing bacteria, and an increase in two mucus-degrading bacteria in the gut of those who ate a fiberless diet (*Akkermansia muciniphilia* and *Bacteroides caccae*). CRC risk factor *Citrobacter rodentium*, a mucosal infection that produces "leaky gut," became more sensitive to mucus breakdown as mucus decomposition increased. Boosting barrier function through increasing claudins and occludins, the proteins that form tight junctions between epithelial cells, is likely to be crucial, as we'll see in the next section. Barrier function is improved and permeability is reduced when *Lactobacillus* and *Bifidobacterium* are present, among other beneficial bacteria [117–120].

7.2. Diet and microbial metabolites

Anti-cancer metabolites and potential oncometabolites can be produced by bacteria in the GI tract from a variety of dietary and digestive components [121]. CRC and other cancers are linked to red meat consumption in a variety of ways, some of which are dependent on the bacteria in the gut. Increased protein levels in the colon can cause DNA alkylation and mutations in the host because many bacteria, particularly some Firmicutes and Bacteroides sp., ferment amino acids into N-nitroso compounds [122]. In this process, nitroreductases and nitrate reductases, which are produced by the bacteria Proteobacteria, are involved and have been linked to inflammation. Carcinogenic heterocyclic amines, which are digested by intestinal bacteria and produce electrophilic chemicals that may cause DNA damage, are particularly dangerous in charred beef [123,124].

The liver produces bile acids, which are then conjugated to taurine or glycine and released into the gastrointestinal tract in order to breakdown red meat's saturated fat. Only around 5% of these primary bile acids make it into the colon, where they are converted into secondary bile acids by the colonic bacteria. Taurine or glycine moieties are deconjugated, and a two-phase dehydration or dehydroxylation process takes place. Deoxycholic acid, for example, can be converted from primary cholic acid by *Clostridium scindens* (DCA). When DCA breaks down cell membranes, it releases arachidonic acid, which is transformed into prostaglandins and reactive oxygen species (ROS) via cyclooxygenase-2 and lipooxygenase, which causes inflammation and DNA damage. Additionally, Taurine can promote the growth of some inflammatory bacteria like *Bilophilia wadsworthia* by promoting the generation of genotoxic hydrogen sulfide [125]. In reaction to consuming red meat, *F. nucleatum* (which is abundant in human CRC) generates hydrogen sulfide [126,127].

GI bacteria transform other food components into tumor-suppressing compounds. For example, dietary fibers are fermented to produce short-chain fatty acids by Clostridium clusters IV and XIVa. A short-chain fatty acid called butyrate is the principal energy source for colonocytes and has been linked to CRC prevention in human metagenomic sequencing studies and gnotobiotic mice models, as has been discussed earlier. It is theorized that butyrate, a pleiotropic chemical, can reduce cancers in a variety of ways. Epigenetically, butyrate influences cell growth and death genes [128]. GPRs associated with tumor suppression are ligands for butyrate [129]. In order to activate TReg cells, butyrate must be able to activate both of these routes. Last but not least, butyrate aids in barrier function of the epithelium, which is critical in preventing inflammation. This can also have a variety of causes. Butyrate oxidation causes a hypoxia-inducible factor 1-based pathway to maintain barrier function, and HDAC inhibition has been shown to promote the expression of tight junction genes including claudins and zonula occludens [130,131]. As a result, daidzein in soy-based products, glucosinolate in cruciferous vegetables such as broccoli (and other isothiocyanates), as well as ellagic acid in certain fruits, are converted to ellagic acid. These are all antioxidants. Most commensal bacteria are neither "good" nor "bad," but rather our diets influence whether our microbiota produces substances that speed or slow tumor formation. Closely related to the group that produces butyrate in response to fiber is Clostridium cluster XIVa member Clostridium scinden, which, when stimulated by fat in the diet, makes secondary bile acids (ClsB) [132,133].

7.3. Cell signaling pathways

Compared to any other gene in CRC, the APC tumor-suppressor gene undergoes the most mutations [134,135]. Numerous cancers of the reproductive tract are caused by loss-of-function homozygous APC mutations, which can lead to nuclear -catenin buildup, aberrant signals from the wnt signaling pathway, and altered expression of downstream target genes such c-MYC. Several animal models of CRC, including those produced by AOM, disrupt the Wnt pathway. Epigenetic suppression of APC (such as DNA hypermethylation of the APC promoter) or opportunistic infection can also affect Wnt signaling. When FadA, an adhesin from *F. nucleatum*, is bound to host epithelial cells, it enhances signaling from -catenin [96]. Exogenous zinc-dependent metalloproteases secreted by ETBF break and destroy the domains of E-extracellular cadherins, enabling for the release of the inhibitory -catenin that would otherwise be inactivated by binding to internal E-cadherins to enter the cell unhindered. c-MYC (avian myelocytomatosis virus oncogene homolog) is a downstream target gene of -catenin nuclear translocation, which promotes proliferation [136]. Bacteria that generate AvrA, which increases -catenin, are linked to hepatobiliary malignancies [103,137].

CRC and other malignancies have an overactive Janus kinase/signal transducer and activator of transcription, which is an important signaling pathway (JAK-STAT). In colorectal cancers, ETBF enhances STAT3 phosphorylation and nuclear translocation [91]. Cellular signaling pathways can also affect the virulence factors of bacteria. In Helicobacter pylori, Src and Abl kinases phosphorylate the virulence component cagA (cytotoxin-associated gene A). Many of the cellular signaling proteins that regulate cell proliferation interact with CagA in distinct ways when it is unphosphorylated [138].

7.4. DNA damage

Carcinogenesis is aided by DNA damage. In the absence of normal DNA repair processes, genotoxins can cause point mutations, insertions and deletions, or chromosomal rearrangements such inversions and translocations if the DNA is damaged by adducts or double-stranded breaks. The DNA of the host cell can be damaged directly by microbial genotoxins. Many Enterobacteriaceae, including *E. coli*, produce colibactin, which induces double-strand breaks in the DNA of their hosts [89,139,140]. Some Proteobacteria produce cytolethal distending toxin (CDT), which causes comparable DNA damage [141].

Free radicals and changes in reactive oxygen species concentrations caused by bacterial metabolites have the potential to be genotoxic in an indirect manner (ROS). *Enterococcus faecalis*, for example, produces a lot of extracellular superoxide (O2) on the luminal side of the intestinal mucosa [142]. The formation of DNA-protein crosslinks, DNA breaks, and point mutations in eukaryotic cellular DNA can cause significant damage from H2O2 created by rapid O2 breakdown. Bacterial

polyamine catabolism pathways are upregulated by ETBF B. fragilis toxin, which results in ROS that damage host DNA and cause colon cancer [143].

Those who eat a diet high in fat produce more bile than those who do not. A variety of studies have showed that bile acids rapidly produce reactive oxygen and nitrogen species, which have been shown to damage the DNA of the host cell (reviewed by Bernstein et al. [144]). Inflammatory bowel disease has been connected to B. wadsworthia, a sulfite-reducing bacteria that thrives in high-fat diets [145].

In contrast to the damaging effects of ROS, repairing damaged intestinal mucosa requires redox signaling. Peptides produced and excreted by microorganisms activate formyl peptide receptors on colonic epithelial cells, resulting in localized ROS formation and activation of redox signaling pathways and migration-associated proteins, which aids in the healing of mucosal wounds in the colon [146]. nicotinamide adenine dinucleotide dinucleotide phosphate oxidase 1 in Lactobacilli promotes epithelial cell proliferation [147].

7.5. Distant sites

Cancer in other regions of the body may be affected by gut bacteria, metabolites, and immune cells traveling through the blood (Fig. 1, Right). The enterohepatic circulation and the hepatic portal vein must be traversed before they can enter the systemic circulatory system and begin their journey there. Hepatic enzymes detoxify potentially toxic endobiotics and xenophores before excreting them [148]. This is important since the liver is the major site for this detoxification. Phase 1 cytochrome P450s functionalize hormones, bile acids, and cholesterol metabolites, which are subsequently conjugated with glucuronic acid or sulfate by phase 2 uridine diphosphate-glucuronosyltransferases or sulfotransferases to form glucuronic acid or sulfate conjugates. Although the kidneys filter many detoxified compounds, others are eliminated into the GI tract via the bile duct, where they become substrates for various microbiological enzyme systems that transform them back into chemicals capable of being reabsorbed or circulated throughout the body to have an impact on distant sites before being sent back to the liver for further processing or eviction. Both human and microbial routes are involved in enterohepatic recirculation, which is crucial in both normal physiology and disease states of the digestive and extraintestinal tracts.

According to a metabolomics study, the microbiota influences the amount of 10% of the chemicals in serum from germ-free and normal mice by 50% [149]. Tumor formation in various parts of the body is influenced by several of these metabolites. If you're concerned about your liver health, you may want to consider supplementing your diet with DCA, which has been shown to increase the risk of fatty liver disease in mice [102]. Cancer prevention molecule Equol from the gut microbiota has been found in several tissues and bodily fluids (including blood, urine, and prostatic fluid) [132]. Endogenous estrogens are broken down in the gut by gut bacteria and have been associated to breast cancer [134,135]. Gut bacteria. For example, studies have shown that inflammatory reactions to Helicobacter hepaticus can lead to the development of breast cancer, and that this can be attributed to a tumor necrosis factor-dependent pathway [150,151]. Bacteria from the environment trigger TLR5 and NF-B in K-ras/p53 mutant mice, which leads to systemic inflammation and tumor formation at many locations [152]. There is a single nucleotide polymorphism in TLR5 that affects the immune response to flagellin and has been linked to long-term survival of ovarian cancer patients. These findings are consistent with this polymorphism [152].

All of the following mechanisms are more likely to work in concert than act separately. *E. coli's pks* pathogenicity island, for example, causes DNA damage but is assisted by chronic inflammation, which is seen in tumor development differences between *pks+ and Δpks+* strains on wild-type genetic backgrounds. In other words, in IL-10 mutant animals, chronic inflammation seems to enhance *pks* oncogenesis. Oncogenesis can be improved by using combinatorial strategies after an initiating event that would otherwise be insufficient to promote transformation [140].

8. Dietary changes can affect the growth of microorganisms and cancer cells

After 10,000 years of agrarian (farmers and pastoralists) life and the Industrial Revolution, a genotype better suited to processing complex carbohydrates from plant-based foods was developed [153]. Plant fiber was broken down by gut microbes in our ancestors' intestines, which allowed them to eat and live. Fermentation, hydrolysis, denitrification, sulfate reduction, and aromatic fission are just a few of the actions that the gut microbiota's enzymes can perform on substances that aren't digested by human enzymes and end up in the GI tract. Because of the abundance of simple and complex carbohydrates, as well as a wide range of other foods, our bodies can now digest them without the assistance of microorganisms. Increasing sugar consumption is one way in which this apparent mismatch in evolution appears to contribute to cancer risk [154].

8.1. Vegetables, fruits, and grains

Fruits, grains, and vegetables provide a wide range of nutrients, including sugars, carbohydrates, dietary fiber, and polyphenolic chemicals. Regular consumption of these plant-based meals has been associated to cancer prevention [155]. The gut microbiota's ability to turn indigestible plant elements into bioactive compounds such as short-chain fatty acids and bioactive phytochemicals has been related to many of the plant components linked to increased health.

Complex carbohydrate and dietary fiber fermentation and hydrolysis produce short-chain fatty acids (acetate, propionate, butyrate) that reach the gut microbiota [156]. For example, butyrate is a critical fuel source for enterocytes in the intestine while propionate regulates glucose and lipid metabolism in the liver [157]. Cell apoptosis, differentiation and hyperacetylation of histones can also be induced by butyrate Butyrate's effects appear to be impacted by the host genotype as well as SCFA concentrations, even though these benefits are intended to prevent cancer from developing and advancing. In a mouse model of colorectal cancer, butyrate was made to concentrate in the nucleus, where it increased histone acetylation and apoptosis, thereby reducing cancer cell proliferation [128]. Butyrate from the microbiome increased tumor cell growth in mice with Msh2 gene alterations, which are crucial for mismatch repair [158]. Excess production of acetate in the gut has been linked to altered insulin regulation and obesity [157,159,160].

Polyphenols, flavonoids, and glucosinolates in plants have all been linked to a lower cancer risk [161–164]. Anticancer isothiocyanates can be made from glucosinolates in cruciferous vegetables by certain bacteria. *Eggerthella spp., Alistipes putredinis, Eubacterium hallii, and Phascolarctobacterium faecium* are microorganisms that digest starch and dietary fibers. Eggerthella and Alistipes degrade starch and dietary fibers [165,166]. Consuming foods low in fiber and hence lacking in polyphenols has been shown in animal models to increase microbial pathogenicity and decrease barrier function [116], however the link between this and an increased risk of cancer remains unclear. Cancer incidence may be reduced by flavonoids including quercetine and apigenin, according to a recent meta-analysis. Toxic and protective pathways associated with isoflavones in soy have been linked to the gut microbiota's ability to access downstream metabolites and nutrients [161,167,168].

8.2. Protein- and fat-containing foods

Organic acids such as phenols, indoles, amines, sulfur compounds, ammonia, and amines can be synthesized from amino acids and proteins [169]. Hydrolysis, deamination, decarboxylation, fermentation, and

elimination are just a few of the processes that result in these by-products. Digestive microorganisms can also break down fatty acids and other lipids, primarily for the purpose of making bile acids. 155, 156] These conversions have been linked to cancer, and they affect the microbiome of the gut as well as liver signaling [170–172].

Carcinogenic fatty acids, such as N-nitroso compounds, have been demonstrated to rise in the presence of high protein and high fat diets [173,174]. An increase in the number of plant polysaccharide-metabolizing microorganisms in animal diets is a result of an increase in secondary bile acid production [175]. Butyrate synthesis and beneficial *Roseburia/Eubacterium rectale* levels in the stools are decreased when low carbohydrate diets are combined with high protein diets [174]. Consuming more fiber does not reduce the risk of colon cancer as much as cutting down on animal products [176]. According to these findings, a diet high in carbs and low in protein may help lower cancer risk.

9. Cancer can be boosted by microbes in a variety of ways

The majority of mouth cancer cases have been connected to tobacco smoking and heavy alcohol consumption. However, in many parts of the world, the incidence of oral cavity cancer appears to be increasing in ways that identified risk factors alone cannot explain. Meanwhile, there has been a surge in interest in the potential links between microorganisms and various phases of cancer formation, and multiple techniques for bacteria and yeast to initiate or accelerate carcinogenesis are currently being researched. According to an increasing body of research, the metabolism and synthesis of carcinogenic chemicals like acetaldehyde may have an etiological role [61].

In developed countries, colorectal cancer (CRC) is one of the most common health issues. CRC risk can be increased by increasing protein and fat intake, for example. CRC is influenced by a variety of factors, including diet. They control the composition and function of the gut microbiota, which produces SCFAs such as propionate, acetate, and butyrate while also having a high metabolic capacity. Butyrate is a major source of energy for colonic epithelial cells and is required for the stability of the gut microbiota and the integrity of the intestinal epithelium. Only a few studies have looked at the anti-CRC capabilities of butyrate [177].

The second most frequent cancer in men and the third most prevalent cancer in women is CRC [178]. Colorectal cancer (CRC) accounts for around 10% of all new cancer cases worldwide. The gut microbiota is a vast bacterial colony that interacts with host cells to regulate a number of physiological functions including energy collection, metabolism, and immune response. It's close to the mucosa epithelium of the colorectal mucosa. In CRC patients, microbial compositional and ecological changes have been documented, and functional investigations in animal models have revealed the importance of a variety of bacteria, including Fusobacterium nucleatum, various *E. coli* strains, and *Bacteroidesfragilis*, in colorectal carcinogenesis. Findings from gut microbiota research have opened up new therapeutic avenues, such as employing gut microbiota tests as biomarkers for screening, prognostication, or forecasting, or altering microorganisms to lower cancer risk, improve medication, or enhance treatment side effects. This research aims to give a complete overview and discussion of the gut microbiota in colorectal neoplasia, including basic mechanisms in microbiota-related carcinogenesis, microbiota as biomarkers for CRC, and the prospect of changing the gut microbiota for CRC prevention or treatment [179].

9.1. Microbes can damage cell DNA, initiating cancer

In recent years, the number of studies looking at the function of the gut microbiome in colorectal cancer (CRC) has exploded. As a result, we now know that particular bacteria (and microbial communities) are found in the stool and mucosa of CRC patients more frequently than in healthy people, including in primary tumors and distant metastases. Although these bacteria are known to cause cancer in animals, little is known about how they interact with colon epithelial cells (CECs) and how these interactions can result in genetic and epigenetic changes that allow tumors to grow and spread. Despite the fact that CRC is becoming increasingly prevalent among younger people, it is still the second leading cause of cancer-related death worldwide. As a result, greater research into the role of gut bacteria in CRC is required. In this paper, we discuss recent improvements in our understanding of the impact of gut bacteria on the genome and epigenome of CECs in connection to CRC [180].

Because only a small fraction of women with known risk factors develop cancer, the changing frequency of breast cancer remains a fascinating topic. According to a new study, both local and distant microorganisms play a role in the genesis, progression, and overall prognosis of breast cancer. A dysbiotic microbiota predisposes the body to cancer by producing genetic instability, starting DNA damage, and perpetuating the damaged progeny by eliciting a positive immune response, metabolic dysregulation, and altered therapeutic responsiveness. Microbiota differences were discovered in healthy people's nipple aspirate fluid and breast survivors'. Secondary metabolites produced by these bacteria may act as signaling mediators in the progression of breast cancer. CRC patients have a 5-year survival rate of around 60%, with 30–40% of patients experiencing recurrence following initial treatment [181].

9.2. Microbes can increase cancer cell proliferation

Despite recent therapeutic breakthroughs, colorectal cancer (CRC) is still the third most common cancer in the United States, with about half of patients acquiring recurring tumors that are resistant to standard chemotherapy. This finding emphasizes the necessity of discovering new chemo-resistance strategies for cancer cells that cause aggressive colon cancers [182]. Patients with CRC have a 5-year survival rate of approximately 60%, with 30–40% experiencing recurrence following initial treatment [183–185].

Both secondary bile acids (SBAs) and short-chained fatty acids (SCFAs), which are both found in the colon, have opposing effects on colonic inflammation when persistently high in physiological levels. Host–microbe interactions need primary BAs, as do cholesterol metabolism and digestion. Biotransformation of primary and secondary BAS occurs in the colon even if they are reabsorbed via enterohepatic circulation. Colonic inflammation and cancer risk factors such deoxycholic acid (DCA) and lithochoholic acid (LCA) are higher in high-fat diets. Fiber consumption is associated to anti-inflammatory and cancer-preventative qualities. The SCFAs acetate, propionate, and butyrate, which are generated in the colon during dietary fiber fermentation, may be to blame for these side effects. The anticancer potential of dietary fiber in the setting of colon cancer caused by a high-fat diet will be better understood if researchers can figure out how secondary BAs and SCFAs influence colonic cell proliferation and inflammation at the molecular level [186].

9.3. Microbes and cancer cells can exchange growth factors

Our bodies allow cells to flourish and evolve in the same manner that ecosystems allow them to do so. Natural selection operates in every ecosystem in the following way: those who survive and reproduce best become a larger proportion of the population's next generation. Cancer develops when cells in the body grow rapidly, monopolize resources, and bypass molecular processes that allow it to function normally [187]. Germs overproliferate, monopolize metabolic resources, and create virulence factors that disturb normal organismal function, just as dangerous bacteria-caused illnesses do [188].

Cancer cells can survive in both the body's ecology and the tumor's microenvironment [189,190]. In the tumor-promoting environment, formation factors, angiogenic signals (signals of blood vessel growth that

feed tumors), and fibroblast "support" cells all play a part [190]. The tumor's microenvironment can aid its development while potentially suffocating it. The microenvironment may aid in cancer suppression if tissue homeostasis is retained and the immune system is not yet dysregulated [191–193].

9.4. Cancer cells and microbes may help each other defend against the immune system

When it comes to our health, bacteria play a crucial role. For example, they play a role in our risk of developing cancer, as both germs and cancer cells depend on incoming nutrients to thrive and multiply. This demonstrates that our food has an effect on cancer cell and microbial cell proliferation, particularly when we consume excessive amounts of energy and minerals. Chemicals produced by cancer cells and microorganisms can influence their growth and survival. These findings underscore the importance of cancer cell-microbial cell interactions in the initiation and progression of cancer [194].

The human stomach is home to fungi, bacteria, viruses, and archaea, including bacteria from the phylum Bacteria. There are many Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria in the environment [195]. By helping to keep the intestinal epithelium intact, microbes can help keep harmful organisms from entering the body and causing disease or injury [196]. Overall, the immune system plays a significant role in cancer. The body's immune system is constantly scanning the tissues for viruses and cancer cells and eliminating any that pose a threat. Human interior organs are protected from potentially harmful cells by immune predation. As prey evolves to evade predators, cancer cells and viruses can evolve to avoid detection by the immune system[197].

9.5. Microbes can raise cancer risk by transforming the intestinal barrier and biofilms that surround It

Inflammatory bowel disease (IBD) is a multifaceted disorder in which genetic, environmental, barrier, and microbial variables interact in the colon, resulting in persistent inflammation. Colorectal cancer (CRC), which contains a subgroup known as colitis-associated malignancies, is more common in IBD patients. Innate immune receptor polymorphism has long been thought to be associated to IBD, and changes in these receptors have recently been found in CRC. Epithelial hyperpermeability, a large number of mucosa-associated bacteria, and a shift in microbial makeup all pointed to a malfunctioning gut barrier (called microbiota) [198].

CRC is a worldwide public health issue with serious human and financial consequences for patients, healthcare institutions, and society. CRC has been linked to oncogenic bacteria such Fusobacterium nucleatum, *E. coli*, and enterotoxigenic *Bacteroidesfragilis*. According to recent studies, before these microorganisms may develop CRC, they must first build biofilms. Gut microbial biofilms are microbial biofilms that form in the mucus layer of the intestine. Biofilm disrupts the intestinal barrier, increases gut permeability, and causes E-cadherin displacement in colonic epithelial cells, all of which contribute to intestinal dysbiosis [199].

Colorectal cancer has been connected to the gut microbiota's onset and progression (CRC). The onset of CRC is driven by local mucosal colonization with certain microbes, according to one common bacterial tumorigenesis explanation (drivers). Changes in the peritumoral environment encourage the colonization of opportunistic (passenger) bacteria, which aids disease progression. Screening for the bacteria that cause CRC's 'driver-passenger' disease could speed up diagnosis and treatment for patients. The revelation that organizing bacterial colonies into higher-order structures called as biofilms is necessary for CRC initiation and growth is changing these efforts [200].

9.6. Proliferation of host cells by microbes can expand their ecological niche

Bacteria populations that create supragingival plaque, subgingival plaque, and tongue coating thrive in the complex ecology of the oral cavity. The properties of the environment dictate which bacteria can dwell there, and the metabolic activities of these microbial communities influence the parameters of the environment. In supragingival locations, saccharolytic bacteria break down carbs into lactic acid, resulting in a brief acidic environment. GCF-produced nitrogenous compounds are metabolized by asaccharolytic bacteria in the subgingival region, resulting in a neutral pH and an anaerobic environment rich in short-chain fatty acids and ammonia. Sulfur compounds, which are the principal components of oral malodor, are produced by asaccharolytic activity against cysteine and methionine in the tongue covering. Changes in environmental parameters may cause individual bacteria to develop adaptive responses to changing environments, potentially allowing more dangerous germs to penetrate the microbial population [201].

Microbes taken from a variety of hosts have been tested to improve the host's survival. The pathogenicity of these bacteria stems from a complicated host-microbe connection in which the immune system is unable to limit microbial multiplication. Candida albicans, Pneumocystis spp., and dermatophytes are some of the human eukaryotic infections that have found a host. These bacteria create infections when the host-microbe relationship is interrupted, such as by medicines, immunosuppression, or changes in their niche, resulting in a greater fungal load. In contrast, a large inoculum can induce disease in healthy people, as proven by a well-known self-experimentation case in which a doctor consumed a Candida albicans solution and got candidemia and candiduria [202].

9.7. Microbes can inspire cells to become more metastatic

As a result, we have a startling dearth of understanding of how metastasis begins. To the best of my knowledge, the century-old notion of cancer cells fusing with tumor-associated leukocytes such as macrophages is the only complete explanation for metastasis that can explain most, if not all, parts of the process, including how it begins. Metastasis, in this view, is a secondary disease that affects the initial tumor cell. The original cell's cell cycle is disrupted, yet it has no desire to leave its source. According to the fusion theory, a healthy migratory leukocyte merges with a primary tumor cell, resulting in the acquisition of a metastatic phenotype. The resulting hybrid, like the original cancer cell, has the ability to travel across the body of a white blood cell while dividing uncontrollably [203].

Pathology analyses of hundreds of human malignant melanoma pathology specimens revealed that autophagy is a common trait, expressed by 85% or more of melanomas, and dermatopathologists refer to it as "coarse melanin" (autophagosomes containing melanosomes and other cytoplasmic material) [204,205]. Finally, think about how fusion might be used therapeutically. New treatment paradigms, such as fusion prevention or death of fused cells based on distinct molecular fingerprints, will surely emerge if fusion is shown to be the cause of metastasis, or at least a component of it [203].

9.8. Microbes produce quantum sensing molecules that may aid in metastasis

Bacteria produce QSMs, which become more prevalent in high-stress circumstances. In contrast to quorum sensing peptides (QSP) and furanosyl borates, which are both produced by Gram-positive bacteria, the majority of N-acyl homoserine lactones (AHL) are produced by Gram-negative bacteria (AI-2 [autoinducer-2], produced by Gram-positive as well as by Gram-negative bacteria). Researchers have discovered that some quorum-sensing molecules are capable of crossing the intestinal barrier and transmitting putative bacterial-host communication signals

[206–209]. The human microbiome's function in cancer progression is still a mystery. Peptides produced by bacteria that are commensal or pathogenic can affect breast cancer cell invasion and, consequently, its prognosis [207].

Quorum sensing (QS) is widely known for its role in microbial pathogenicity and antibiotic resistance. QS regulates motility, swarming, and biofilm growth by using signal molecules such as acylatedhomoserine lactones (AHLs) produced by bacteria at a specific population density. Inhibiting QS may reduce pathogenicity, antibiotic resistance, and biofilm development in both systemic and local illnesses. In many bacteria, homoserine lactones and other transmitters increase antibiotic resistance and pathogenicity; thus, inhibiting QS signals reduces resistance and virulence [210].

A high mortality rate owing to metastases makes colorectal cancer one of the most common malignancies in the world. As according metagenome-wide comparisons of healthy persons with cancer sufferers, the human intestinal microbiota may be involved. As a result, however little known about the chemicals produced by microorganisms that are engaged in communication between them. Quorum sensing peptides have yet to be studied in this microbiome-host interaction; neither their presence in vivo nor any in vivo host effect has been reported [211].

9.9. Microbes modify cancer cells using epigenetics to boost the proliferation of cancer cells

The microbiota has an impact on many diseases, and it plays a role in their progression and suppression. In order to sustain a healthy human physiology, the connection between the host and the microbiota must be balanced. An unbalanced microbiome puts the human body at greater risk of immunodeficiency and cancer than a balanced microbiome does. Many bacteria have been linked to cancer, but little is understood about how microbial interactions effect gene and epigenome modifications, as well as how tumor growth is sparked or sustained. Several studies have found that microbes in the stomach can change DNA methylation, DNA repair, and DNA damage in some way or another. Cancer-related genes and pathways, particularly those involved in cell development and signaling, are affected by the bacteria in the gut. These studies look at various chemopreventive agents in cancer prevention and treatment along with promising microbiome molecular targets which promote carcinogenesis, epigenetic changes of various potential targets caused by altered microbiota and current research on dysbiosis and the colon, lung, ovarian and breast cancers and their treatment [212].

Researchers and doctors have recently paid more attention to dietary therapy for colon cancer prevention. Probiotics are gaining popularity as potential medicinal agents as well as nutritional and healthful food supplements. The probiotic metabolome may influence a variety of cellular and molecular processes, including colon cancer initiation and progression. Probiotic metabolites affect cellular signaling and metabolic processes in a variety of ways. In the gut, microbial metabolites interact with a wide range of metabolic targets that regulate cell proliferation, differentiation, death, inflammation, angiogenesis, and metastasis (organic acids, bacteriocins, peptides, and so on). Progress in this field predicts that, in the not-too-distant future, epigenetic modifications will be used to treat colon cancer on a daily basis. The current research focuses on the molecular underpinnings of individual probiotic metabolites' therapeutic and chemopreventive actions, as well as the links between probiotic metabolites and the molecular signaling cascades hypothesized to be epigenetic targets in probiotics [213].

10. Key carcinogenic organisms' mechanistic studies

For example, the human papillomavirus and the hepatitis B virus will not be discussed here. The germs Helicobacter pylori and Fusobacterium nucleatum are the most commonly associated to cancer. In many of the cancer-causing groupings described by Hanahan and Weinberg, detailed examinations of the actions of these species, among others, continue to uncover new pathogenetic pathways [87].

Over millions of years, humans have developed alongside a complex bacterial, fungal, and viral microbiome. Some well-known epidemiological correlations between certain bacteria and cancer have been discovered at the cellular level. Research on microbiomes like the human gut microbiome has been greatly aided by advances in next-generation sequencing technologies, which have allowed taxonomic and metabolic links between microbiome and cancer to be discovered. Using direct and immunological techniques, these research have discovered causal pathways for both microorganisms within tumors and bacteria in diverse host habitats far from tumors [38].

Hundreds of microorganisms interact with the eukaryotic host, both resident and transient, affecting critical physiological pathways. New research shows that host–microbe interactions play a role in tissue homeostasis, cell fate decisions, and regeneration potential in epithelial barrier organs like the skin, lungs, and gut. In humans and animals, malignant tumors of various organs have been reported to have a different microbiome. Changed metabolic characteristics and released chemicals have been linked to epithelium carcinogenesis and tumor growth in mechanistic studies. According to recent research, connected microbial communities have a considerable impact on the response to chemotherapy and immune-checkpoint inhibitors during cancer treatment, suggesting that microbiota manipulation could be an effective method in personalized oncology [214].

10.1. Genotoxic and non-genotoxic bacterial toxin

Chemicals are an inescapable aspect of contemporary life, and some of them can be harmful to people's health. Many countries are concerned about chemical carcinogens, and international organizations like the World Health Organization have lobbied for legislation. Carcinogens are currently classified as genotoxic or non-genotoxic, with each group having its own set of rules. The genotoxic chemicals that cause cell mutations cause cancer. No safe exposure threshold or dose has been established due to their ability to interact with DNA. They are prohibited because even low amounts of genotoxic ants can cause cancer in humans. Non-genotoxic carcinogens are assumed to have a safe exposure threshold or dose since cancer is produced by causes other than mutations, such as hormonal influences, cytotoxicity, cell proliferation, or epigenetic alterations. As a result, its use in society is accepted as long as the amount of exposure or consumption does not exceed the permissible limit. Genotoxicity tests aid in the differentiation of the two categories of carcinogens [215].

A total of 62 compounds were chosen from three categories of test chemicals. The Green Screen HC assay was used to screen these compounds, and the results are included in this report. Multiple operators reproduced all of the experiments, including those with and without S9. Group 1 chemicals should pass in vitro mammalian cell genotoxicity testing: GreenScreen HC dependably positive 18/20 (90%) of the samples. In vitro tests for genotoxicity on Group 2 compounds should come up negative: GreenScreen HC consistently produced negative results in 22 of 23 cases (96%). Groups 1 and 2 have a total concordance of 93%. Despite the fact that Group 3 compounds should show no chromosomal abnormalities or Tk mutations in mammalian cells in in vitro genotoxicity experiments, they have been observed to cause them in mouse lymphoma cells, frequently at high doses or cytotoxicity levels: Green Screen HC consistently produced poor results 13/17 (76%) of the time [216].

The use of Bacillus thuringiensis toxins as biopesticides in biological insect control and transgenic plants has enhanced their environmental availability. All -endotoxins from B. thuringiensis, cry 1Aa, cry 1Ab, cry 1Ac, and cry 2 A, were examined in zebrafish Danio rerio to see if they had any negative effects on their genome or embryos [217]. Hematopoietic stem cell transplantation may help patients with hemoglobinopathies, congenital immunodeficiencies, and other disorders including

AIDS (HSCT). Despite the fact that employing genetically corrected cells in autologous HSCT reduces the risk of graft-versus-host disease (GVHD), conditioned genotoxicity is still a big problem. We created an internalizing immunotoxin that effectively trains immunocompetent mice by targeting the CD45 receptor, which is only found on hematopoietic cells [218].

10.2. Toxic inflammation, rapid cell growth, and a weakened immune system are all caused by fusobacterium

CRC is the third most common cancer worldwide, and its etiology has gained a lot of attention in recent decades. Microorganisms found in the gastrointestinal system have recently been identified as possible etiological agents. Fusobacterium and CRC, in particular, have been found to have a direct proportional relationship. Since then, a variety of animal models have been employed to examine Fusobacterium's functional role in CRC formation. Despite the fact that several epidemiological research have failed to show a direct link between Fusobacterium and CRC, multiple pathogenic pathways have been established that cause the disease. Due to its high adhesive and invasive capabilities, Fusobacterium can stimulate the E-cadherin/-catenin It's been linked to epigenetic abnormalities such microsatellite instability (MSI) and hypermethylation, which can lead to epithelial cell malignancy. Fusobacterium can change the tumor microenvironment (TME) by recruiting and suppressing myeloid-derived suppressor cells (MDSCs), tumor associated macrophages (TAMs), and tumor associated neutrophils (TANs) (TANs). This article delves into the connection between Fusobacterium and colorectal cancer. Potential therapeutic and prevention options for colorectal cancer associated to Fusobacterium are also considered in light of the introduction of microbiome-based medications. CRC is the third most common cancer in the world, and its etiology has gotten a lot of attention in recent decades. Microorganisms found in the gastrointestinal system have recently been identified as possible etiological agents. Fusobacterium and CRC, in particular, have been found to have a direct proportional relationship [219].

Inflammation is the body's natural response when tissue homeostasis is disrupted. At all stages of tumor development and treatment, chronic inflammatory processes have an impact. The major cellular and molecular mechanisms that coordinate inflammation's tumor-promoting and tumor-antagonizing effects are outlined in this Review, which investigates the relationship between cancer growth and inflammatory processes. We also investigate the recently postulated role of commensal bacteria in inflammation-induced cancer, arguing that a better understanding of this microbial influence is essential for modern cancer treatment targeted therapy [220].

A dysbiotic bacteria causes periodontitis, which is a serious bacterial illness. New information on the genesis and stability of dysbiotic oral microbial communities that can induce inflammatory disease in both local and remote places has recently been discovered, according to new research. The strategies of microbial immune subversion that tip the balance from homeostasis to sickness in oral and extra-oral locales are discussed in this work [221].

10.3. Both lymphoma and gastric epithelial disease are linked to H. Pylori

Human stomach cancer and gastric mucosa-associated lymphoid tissue lymphoma were the first diseases linked to Helicobacter pylori. *H. pylori* cagA-positive strains appear to be important in mammalian cell neoplastic transformation, according to accumulating evidence [222]. Bacteria produce the CagA protein, which binds to and activates the pro-oncogenic phosphatase SHP2 in an improper manner. CagA-SHP2 interaction requires the Glu-Pro-Ile-Tyr-Ala (EPIYA) motif on tyrosine. Japan, China, and Korea have some of the highest incidences of stomach cancer in the world. The majority of Helicobacter pylori strains in East Asia produce an East Asian CagA variant (EPIYA-D) that lacks the SHP2-binding EPIYA motif found in CagA from other parts of the world. EPIYA-D has a twofold greater interaction with SHP2 than EPIYA-C [223].

Helicobacter pylori infection has been associated to gastric mucosal lymphoma and distal gastric cancer in humans. Because of the use of a combination of medicines to remove H. pylori, most cases of gastric lymphoma are cured, and the growth of stomach adenocarcinoma is halted. H. pylori causes a long-lasting inflammatory response in the stomach, which promotes gastric neoplasia. This chronic inflammatory state causes persistent oxidative stress and adaptive changes in the pathobiology of stomach epithelial and immunological cells in a small percentage of infected patients, eventually leading to outright neoplastic transformation [224].

11. The cancer curing potential of the microbiome and its components

The human gut microbiome has an impact on many host systems, including metabolism, inflammation, and immune and cellular responses. The microbiome is rapidly becoming recognized as a factor in the onset of cancer. Altering the gut microbiota increases the host response to cancer treatment in preclinical models; the gut microbiome has been shown to be altered in a range of illnesses, including cancer. Using microbial organisms or their products to treat cancer offers the added benefit of shrinking tumors. By stimulating bacteria to create potentially cancer-causing toxins and metabolites, the microbiome, on the other hand, may have a negative impact on cancer prognosis. As a result, future anticancer medicines may combine microbiome management and its products with immunotherapeutics and other more traditional techniques that target malignant cells directly [225,226].

Next-generation sequencing has given us unprecedented access to the genomes of tumors, hosts, and the many microbes that live inside living things thanks to this new technology. These bacteria may give sensitivity to specific malignancies and may potentially modify therapy response, according to growing findings. The fact that gut bacteria influence therapeutic responses in preclinical models and patient cohorts exemplifies this. On the other hand, these microorganisms may have an impact on treatment responses as well as treatment-related harm. As a result of these circumstances, microorganisms are increasingly being used to treat cancer and other disorders [227].

Microbiota play a role in cancer susceptibility because they reside in high numbers in the human body and have a dramatic impact on immune cell activity. In 15–20% of cancer instances, microbial infections are the cause. According to microbiome studies utilizing metagenomic sequencing, a changed composition of commensal microbiota is linked to an increased occurrence of malignancies (dysbiosis). A preclinical study employing gnotobiotic mice models that are colonized with one or more particular bacteria reveals a causal role for alterations in the microbiota in cancer. Inflammation, DNA damage, and the production of chemicals linked to oncogenesis and tumor suppression have all been linked to the microbiota's influence on cancer susceptibility and progression, according to these findings [105].

11.1. Specific bacterial products in cancer therapy

The use of live microbes in cancer treatment has a lot of potential. In recent years, the number of genetically engineered bacteria with therapeutic and diagnostic applications has risen. Purified bacterial products, on the other hand, are gaining traction as novel bioactive product classes for treating and preventing cancer spread and growth. Using immunotoxins, proteins, and peptides as a focal point, the first section of the essay examines the most recent studies on using live bacteria as well as their products as anti-cancer medications. Using azurin or a peptide derived from those as anticancer treatments will be the focus of this discussion. The second half of the paper discusses the difficulties of using metagenomic techniques to find new anti-cancer drugs derived from bacterial sources [228].

Nanomedicines [229] derived from biologically produced vesicles can be used to target specific cells, thanks to advances in genetic engineering technology. Cancer cells can be targeted and killed with siRNA that is delivered via bioengineered bacterial outer membrane vesicles (OMVs) with low immunogenicity (KSP). In order to create OMVs that are more specific to human cells, a mutant strain of Escherichia coli was used that had a lower toxicity to human cells. In a mouse model, siRNA-packaged OMVs injected systemically resulted in targeted gene silencing and significant tumor growth regression. There were no negative consequences to the new OMVs, which were also well-tolerated. For cancer treatment, we believe bioengineered OMVs offer a great deal of potential [230].

Cancer, which is the biggest cause of death in the twenty-first century, is one of humanity's most feared diseases. New cancer therapies are desperately needed due to the pharmacological adverse effects of standard chemotherapy, radiation, and surgery. Other strategies, such as cancer vaccinations and biological therapies, have been shown to be very helpful in the treatment of cancer, in addition to regular drugs. The low toxicity of these new cancer drugs, as well as their ability to target and destroy cancer cells, may account for their effectiveness. For more than a century, bacteria have been utilized to cure cancer. Live, attenuated, or genetically modified anaerobic bacterial species can infiltrate and flourish inside tumors, halting tumor development. In target specific therapy, bacteria and their spores are used to deliver prodrugs and other proteins to tumors [231,232].

11.2. The microbiome as a modulator of chemotherapy

In recent decades, cancer treatment has evolved from surgery, chemotherapy, and radiation treatment to include targeted medications and immunotherapies. In spite of the discovery of innovative medicines targeting certain cancer-related genetic factors, and also more recent time immune system-modulating biologics, focused therapies continue to benefit only individuals with particular cancer subtypes, and there is still opportunity for better survival outcomes. There have been numerous biomarker studies undertaken as a result of the high rate of treatment failure in clinical practice to identify the features that contribute to disease relapse and therapeutic interventions failure. There is an urgent need for more research into the gut microbiome's role in cancer prevention and treatment because it has long been proven that microbiota fundamentally alter mammalian immunity [233].

Thousands of years have passed since humans and their commensal microorganisms co-evolved. The microbiome influences human health and has been linked to a variety of illnesses, including cancer. Thanks to advancements in next-generation sequencing technologies, our understanding of the microbiome's function in cancer and cancer therapies has vastly improved. The microbiome and the pharmacological effects of chemotherapy and immunotherapy have been revealed in a new study. As a result of chemotherapy, the immune system is suppressed and the variety of the microbiome in the body is reduced. The human microbiome, particularly the gut microbiota, regulates the efficiency of chemo-drugs by metabolic and enzymatic breakdown, ecological changes, and immunomodulation [234].

The gut microbiome, urogenital microbiome, and skin microbiome have all gotten a lot of press recently. The microbiota of healthy breast tissue and breast illnesses, on the other hand, is poorly understood. Each patient's breast tissue, nipple aspirate, and gut bacteria have their unique microbiome, according to the research, with some species predominating in breast tissue. The breast microbiome and related microbiomes may also influence therapy response and could be employed as biomarkers for early breast cancer identification and staging [235].

11.3. Microbial modulation of immunotherapy efficacy

For patients with metastatic disease, immune checkpoint inhibitors, which have been discovered in recent years, have revolutionized cancer therapy. And from the other hand, immunotherapy comes with a wide spectrum of adverse effects, the majority of which are temporary. Worse, a significant percentage of cancer patients are resistant to such treatment. It's taken a long time to find precise biomarkers that can predict clinical responses to immunotherapy. Unfortunately, such instruments do not exist, and our understanding of the mechanisms behind their efficacy and safety is limited. Human health and illness outcomes are increasingly influenced by the microbiome, which is becoming more well recognized. Microbes interact with host cells and cytokines in a variety of ways to create an inflammatory environment that is either pro- or anti-inflammatory. Microbes appear to influence the efficacy and toxicity of immunotherapy by changing the host's local and systemic immune responses, according to recent research [236].

Several diseases, including cancer, have been related to the activities of the commensal microbiota, which has a significant impact on human health. There are many ways in which the microbiome influences host physiology and immunological responses in gnotobiotic animal models. According to a recent study, the microbiome can have a more targeted impact on cancer treatment outcomes. In animal trials, therapeutic interventions that improve microbiome composition to promote immunotherapy responses have showed promise. Early-stage clinical trials are increasingly using these preclinical discoveries [237].

12. Possibilities and obstacles in cancer treatment due to microbiome interactions

We've learnt about a spate of negative interactions between the microbiota and medical interventions like drugs, radiation, and surgery over the last decade of microbiome study. What if we could manipulate our microbiomes to prevent such occurrences? This review discusses methods for reducing negative microbiome effects as well as applications from the emerging field of microbiome research. We look at circumstances when the microbiome has a direct impact on a treatment, such as changes in pharmaceutical metabolism, as well as cases where the microbiota is directly modified by a treatment, such as radiation therapy. \ Understanding and minimizing microbiome-related adverse events is a complex task that will necessitate a data-driven approach that incorporates causal statistics, multiomics approaches, and a tailored approach to minimize negative consequences. We discuss many research considerations for successful microbiome adverse event avoidance, as well as the various challenges and opportunities that lie ahead [238].

Immunotherapy has been used to treat cancer for a long time. However, the vast majority of cancer patients do not benefit from these treatments at the moment. The majority of solid tumors have circulatory abnormalities that help them elude detection by the immune system. High levels of proangiogenic agents like VEGF and angiopoietin 2 are to blame for these problems (ANG2). Because rectifying the abnormal tumor vasculature can boost immune effector cell infiltration and convert the fundamentally immunosuppressive VEGF, using drugs that target these molecules with caution can improve therapeutic response. Immunotherapy requires the recruitment and activation of immune effector cells in the TME, and immunological responses and vascular normalization appear to be linked. Antiangiogenic medicines used with immunotherapies may improve immunotherapy efficacy while lowering the likelihood of immune-related side effects [239].

12.1. Can we boost the immune system in order to disrupt microbe-cancer cell collaboration?

Fungi, bacteria, viruses, and archaea live in the human gut, which is a complex ecosystem that includes bacteria from the phylum Bacteria [195]. The bulk of bacteria are Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria. It is possible that microorganisms can help to preserve intestinal barrier integrity and prevent potentially harmful organisms from invading the epithelium and triggering illness or injury [196]. Changes in the DNA of human somatic cells, alterations in cell

cycle regulation and the promotion of cell proliferation by microbes all have the likely to improve cancer risk. Ten to twenty percent of all microorganisms are estimated to be responsible for human malignancies [41]. The International Agency for Cancer Research has designated ten bacteria as carcinogenic, with Helicobacter pylori being one of them [41].

Our bodies function as ecosystems that allow cells to thrive and evolve. Natural selection operates in every ecosystem in the following way: the players that survive and reproduce the best become a larger percentage of the population's next generation. Cancer is generated by the body's cells quickly replicating, monopolizing resources, and bypassing molecular systems that allow it to function normally [187]. Microbial disturbances and serious bacterial illnesses are caused by overproliferation of microbes, which monopolize metabolic resources and generate virulence factors that disrupt normal organismal function (dysbiosis) [188].

12.2. Is it possible to treat cancer by using certain microbes to regulate the population of cancer cells?

The importance of the microbiome in cancer initiation and development is becoming recognized. Antibiotics and probiotics have been demonstrated to boost cancer therapy efficacy in some circumstances, but worries about collateral damage to the microbiome and consistency have encouraged study towards emerging microbiome–cancer interfacility systems. In light of nanotechnology's success in revolutionizing cancer diagnostics and treatment, nanotechnologies having the capability of controlling interactions that take place throughout all microscopic and molecular parameters in the microbiome and tumor microenvironment could provide novel cancer treatment strategies. As a result, the nexus of nanotechnology, microbiota, and cancer has a lot of promise. We identify important areas where nanotechnologies can be utilized to regulate the microbiome for cancer treatment in this Review, present an outline of basic research, and discuss potential challenges and our prognosis on this rapidly growing issue [240].

Leukemia, lymphoma, and other cancers affect around 15,000 American children and adolescents mostly under age of 19. Chemotherapy will be given to all children and adolescents with acute leukemia as part of their treatment. Fortunately, throughout the last three decades, most pediatric cancer survival rates have improved considerably, with an overall survival rate of above 90%. The survival rate differed significantly depending on age group (94% for those aged 1–9.99 years, 82% for those aged 10 years, and 76% for those aged above 15 years). Almost three out of four occurrences of juvenile leukemia are caused by ALL. Preventive or therapeutic use of antibiotics in combination with chemotherapy may have long-term effects on the gut microbiota. Unfortunately, little is known about how treatment affects the microbiota of children and adolescents who have been diagnosed with leukemia. Prior to and following chemotherapy treatment, we compare the gut microbiota of patients with acute leukemia to that of their healthy siblings, using 16S rRNA marker gene sequences [241].

12.3. Can commensal microbes enhance the effectiveness of therapy?

Gut bacteria influence the therapeutic response and toxicity of cancer treatments such as cytotoxic chemotherapy, radiation therapy, kinase inhibitors, and immunotherapy therapies. The gut microbiota produces short-chain fatty acids that are critical regulators of histone post-translational modifications that alter gene expression, thus linking the microbiome to cellular metabolism and transcriptional regulation. Cancer and its treatments affect the microbiota, resulting in dysbiosis. This can make it harder for a patient to respond to treatment and enhance the drug's systemic negative effects. In addition to the gut microbiota, microbes have been found in tumors that can impact chemotherapeutic treatment response and result in immune suppression [242].

Antibiotic resistance genes (ARGs), such as those encoding -lactamase enzymes (BLA), which break down routinely used antibiotics like ampicillin, can be found in the complex bacterial communities that make up the gut microbiota. Antibiotic use has risen in both human and cow populations in recent years, increasing the prevalence of such genes in commensal bacteria [243].

13. Future directions and challenges

Dysbiosis and cancer have been linked because of the presence of microbes in the digestive tract and tumor tissue. As cancer progresses, major microbiota differences among normal and cancerous tissue can aid in the identification of dysbiosis indicators (grade, stage, and metastasis). Understanding dysbiosis may also aid in answering why some persons with similar clinical characteristics have varied disease progression and treatment responses. Several bacteria have been identified as possible tumor cell modulators, either directly or indirectly through toxins produced. Many of the microbiota's "alpha bugs" were found to be dominant, allowing potentially harmful bacteria to enter as "passenger." Finding out what causes these diseases and developing better ways to diagnose and treat them are the apparent next steps. The goal is to push dysbiosis toward eubiosis by changing the microbiota by dietary modifications, prebiotics, probiotics, symbiotics, and postbiotics. Some of the emerging efforts to boost therapy responses in cancer patients include FMT, a lab-grown microbiome consortium, and modified microbes. Microbiome research, while interesting, comes with its own set of problems. Because the composition of the microbiota can fluctuate with geography, age, eating patterns, BMI, prescription medicines, antibiotics, and pet ownership, the study cohorts must be carefully designed and all relevant variables must be included in statistical analyses. Preservation of the original microbiota and prevention of contamination during sample collection and analysis are two other important considerations for microbiome research.

Several research [244–249] have investigated the impact of sample storage conditions on microbiota, such as preservatives and temperature, and showed that changes owing to storage conditions are small when compared to individual participant variances. It is critical, however, to select storage settings that limit changes to the original microbiota and to adhere to these for all study samples. Contamination of samples by laboratory chemicals' DNA is another issue, particularly for samples with low microbial quantities. As a result of the discovery of "kitomes" (or contamination genomes) in DNA extraction kits, [45,250] it is strongly recommended that microbiome samples be processed using the same batch of extraction kits or to consider "different kits" as a variable. Positive and negative controls, as well as well-vetted positive controls, are used during sequencing in order to evaluate the contaminated background. If a study has a limited number of participants or a complex research issue, it is necessary to conduct validation cohorts to ensure that the findings from discovery cohorts can be substantiated. Microbiome research standards and recommendations are now being created [251]. The European Commission's META genomics of the Human Intestinal Tract (MetaHIT) project and the National Institutes of Health's Human Microbiome Project, which included 15 institutes from eight countries, created and published good clinical practice criteria for microbiome research [252,253]. Microbiome Quality Control is a collaborative effort that evaluates experimental designs in order to help the microbiome sector develop best practices [254]. Human microbiome research is paving the way for cancer risk assessment and the creation of novel preventative and treatment options, thanks to major technological advancements and the adoption of universal standards.

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