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Review Article

The Microbial Conductor: A Conceptual Framework for Understanding Cancer Hallmarks through the Intratumoral Microbiome

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Abstract

The intratumoral microbiota, which includes various communities of bacteria, fungi, and viruses within the tumor microenvironment, is increasingly regarded as a multidimensional factor in cancer biology. In this review, the concept of a “microbial conductor” is presented as a conceptual framework for understanding how microbial communities may influence multiple hallmarks of cancer. The intratumoral microbiota exhibits substantial heterogeneity across individuals and is strongly associated with host immune responses, the tumor microenvironment (TME), and therapeutic responses. Current evidence suggests that intratumoral microorganisms are associated with tumor progression across multiple cancer types. Mechanistic studies have demonstrated that specific microbial taxa can modulate proliferative signaling, immune evasion, genomic instability, inflammation, and metabolic reprogramming through distinct molecular pathways. Furthermore, emerging clinical evidence indicates that microbiome composition may influence prognosis and treatment response, although validation in large-scale prospective studies remains limited. Importantly, the current body of evidence ranges from associative observations to mechanistic investigations and limited clinical validation, highlighting the need for further studies to establish causal relationships and therapeutic interventions in targeted oncology approaches.

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Introduction:

The human microbiome is made up of microbes, which include bacteria, fungi, and viruses. Humans live alongside these microbes in a symbiotic relationship. They can be found at different locations within the human body. These microbes prefer areas with mucous membranes such as the skin, genitourinary tract, mouth, and gastrointestinal tract, with the gastrointestinal tract being home to most of the bacteria (1). Furthermore, microbial colonization has been reported in previously thought-to-be sterile tissues such as the thyroid gland, pancreas, and liver (2, 3, 4). The unique makeup and biological function of each microbial population are intimately linked to human health and illness. To date, many significant findings have been reported regarding the intratumor microbiota (Figure 1). Recent studies have revealed that the local microbiota plays an essential role in the tumor microenvironment across different cancers, especially mucosal cancers, such as lung, skin, gastrointestinal, and nasopharyngeal cancers (Figure 2). For instance, it is important to note that the compositions of bacterial communities vary within tumors. The microbial community profiles were examined in 1,526 specimens taken from seven types of cancers in humans, and researchers reported remarkable variations in terms of their composition and abundance compared with the microbial content in normal tissues adjacent to tumors (5). In another clinical study carried out among 507 patients with lung cancer, the intratumoral bacterial abundance was found to be an important marker for determining the prognosis of the condition (6). Intratumoral microbial communities differ in composition and abundance from one type of tumor to another, affecting different processes in carcinogenesis and metastasis. Understanding the intricate relationship between microorganisms and tumors could aid in the assessment of current cancer treatments tailored to individual patients while providing insight into possible treatments in the future (3, 5). In this review, we present the essential theoretical basis of the "microbial conductor" hypothesis to examine the role played by the tumor microbiome in tumor development and progression. Rather than depicting the microbiome as mere bystanders, this review proposes a conceptual framework describing microbiome-mediated regulation of cancer hallmarks through the use of signaling molecules and metabolites as a weapon to achieve either tumor-promoting microbial imbalance or tumor-suppressive microbial equilibrium. On the basis of this conceptual framework, the clinical implications arising from these findings are discussed.

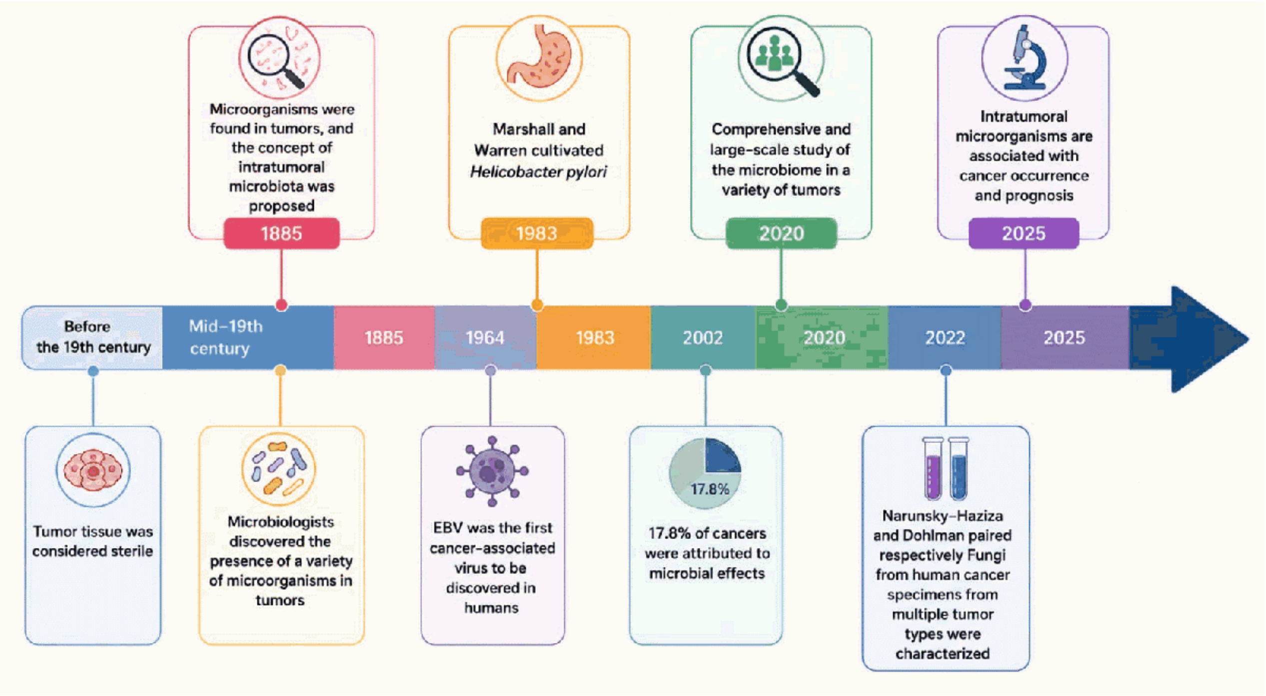

Figure 1: Landmark events in the study of the intratumoral microbiota. Timeline of the most significant milestones in the history of discoveries related to the intratumoral microbiota.

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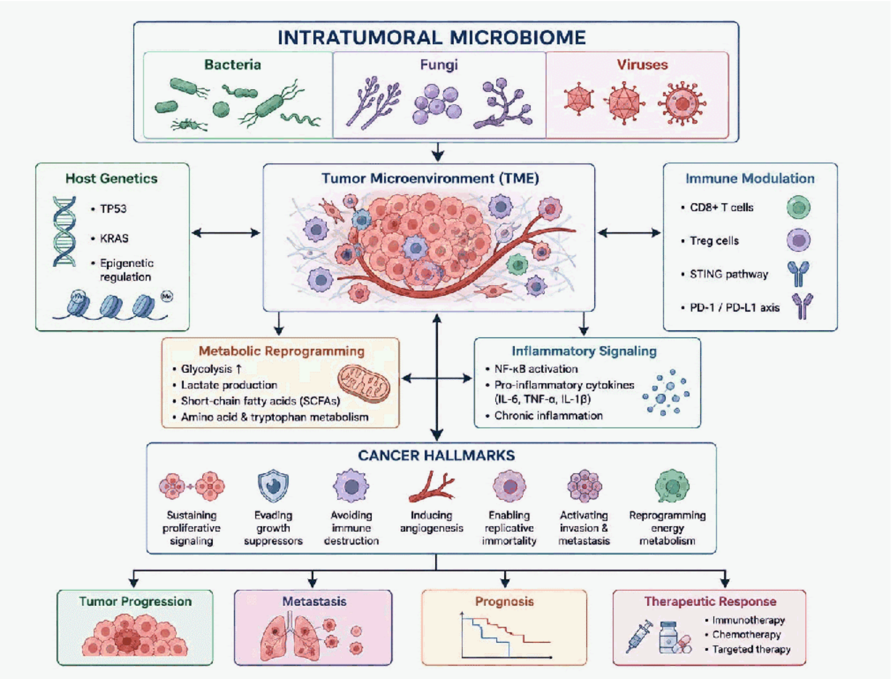


Figure 2: Schematic representation of the proposed “microbial conductor” framework. The intratumoral microbiome, comprising bacterial, fungal, and viral communities, interacts with the tumor microenvironment through the modulation of host genetics, immune regulation, inflammatory pathways, and metabolic reprogramming. These interactions collectively contribute to multiple cancer hallmarks and may influence tumor progression, metastasis, clinical outcomes, and response to therapy.

* Created by the authors using Canva Pro. Conceptually derived from Wu et al. (2026) and additional literature describing interactions between the intratumoral microbiome, tumor microenvironment, host immunity, and cancer hallmarks. This figure represents an original reinterpretation and was not directly reproduced from any previously published figure.

Literature search strategy

The literature for this narrative review was searched in the PubMed, Scopus, Web of Science and Google Scholar databases. The relevant publications published from 2000 to 2026 were searched by combinations of the following keywords: tumor microbiome, tumor microbes, cancer traits, microbiome and cancer, tumor microenvironment, microbial carcinogenesis, immunotherapy for cancer, tumor bacteria, tumor fungi, and tumor viruses.

Peer-reviewed primary scientific research articles, mechanistic studies, translational studies, clinical studies, and quality review articles addressing the relationship between the microbiome and cancer were favored as sources. Additional literature was found by manually searching the reference lists of important papers.

Studies that focused on the role of intratumoral microbes in cancer development, progression, and metastasis; the regulation of immune responses; therapeutic responses; and interactions between the host and the microbial community were selected for inclusion. Abstracts from conferences, non-English articles, duplicates, and studies with insufficient methodological information were not included. Owing to the fast-developing pace of research, attention was especially given to more recent publications, but important seminal papers were also considered.

Novelty and Scope of the Present Review

However, although extensive research has investigated the association between the microbiome and cancer, much of it has been limited to a specific group of bacteria, fungi, and viruses; a particular type of cancer; or one of the many mechanisms involved in tumor development. This study offers a novel approach, aiming to understand the diverse components of the tumor microbiome as “multidimensional support” for the underlying structure of cancer. By presenting evidence related to bacteria, fungi, and viruses, this study provides insight into how the polymorphic microbiome can contribute to the regulation of several key tumor features, including proliferation signaling, immune evasion, metabolic reprogramming, genomic instability, hematopoiesis, invasion, metastasis, and treatment response.

Furthermore, particular attention is given to the influence of the microbiome on tumor development, tumor microenvironment remodeling, and immune-associated genetic regulation. The available evidence to date linking the microbiome to cancer is also being evaluated, distinguishing between correlated findings, explanatory evidence, and mechanisms related to the existence of such a link, as well as the possibility of applying therapeutic strategies on the basis of it and how to overcome problems controlling their use.

Intratumoral Microbiome as a Microbial Conductor:

Given the above, the intratumoral microbiome cannot be regarded as a second player or a static participant in such processes. Instead, this review proposes "microbial conductor" as a conceptual framework for understanding how the intratumoral microbiome may influence multiple hallmarks of cancer. Within this model, microbial communities are viewed as potential modulators of tumor-associated processes through diverse molecular, metabolic, and immunological interactions. While accumulating evidence supports these associations, the extent to which the microbiome directly orchestrates cancer hallmarks remains an active area of investigation (7).

Despite accumulating evidence, causality remains controversial:

While numerous studies have indicated a significant association between the microbiome found within tumors and cancer progression, this topic remains controversial. Particular attention is given to the influence of the microbiome on tumor development, tumor microenvironment remodeling, and immune-associated genetic regulation. Thus, it is difficult to generalize the results obtained from such studies to human beings. Additionally, most studies have used correlation approaches; hence, it remains unclear whether the microorganisms in question are a cause of cancer development rather than an effect caused by changes in the tumor microenvironment (8).

Quantitative Insights and Evidence Synthesis

While most research on the intratumoral microbiota is based on qualitative data, there are instances where quantification has led to significant revelations regarding the importance of microbial activity within tumors. Large-scale meta-analyses have revealed that bacteria can be found in almost all tumor types studied, with significant differences in the number and variety of microorganisms in various forms of cancer. Clinical studies have shown that approximately 15% to 20% of cancers can be attributed to the involvement of microbes (8).

On the other hand, studies have linked the presence of certain microbiome components with better or worse responses to immunotherapy. The microbiome composition of cancer patients varies because of their varying responses to the use of PD-1 inhibitors. Furthermore, a more diverse microbiome has been linked to higher survival rates. Nonetheless, these studies are still inconclusive owing to inconsistencies in methodology and approaches to analyses used in such studies. Hence, more uniform quantitative studies, such as meta-analyses and multicenter data, are needed to help establish the actual role of the microbiome in the development and treatment of cancers (5, 9).

Using the microbial conductor as a framework to orchestrate cancer hallmarks

The concept of "hallmarks of cancer" offers a critical foundation for understanding the biological capacities that are developed in the process of carcinogenesis. The "hallmarks of cancer" theory was initially proposed by Hanahan and Weinberg (10, 11). It defines the essential characteristics required for tumor progression and metastasis, such as self-sustaining proliferation, evasion of growth inhibitors, resistance to apoptosis, limited replication potential, induction of angiogenesis, metastatic spread, alterations in metabolic pathways, evasion of immune responses, inflammatory tumor promotion, genetic instability, acquisition of plasticity, nongenomic epigenetic modifications, polymorphic microbiota, and cellular senescence.

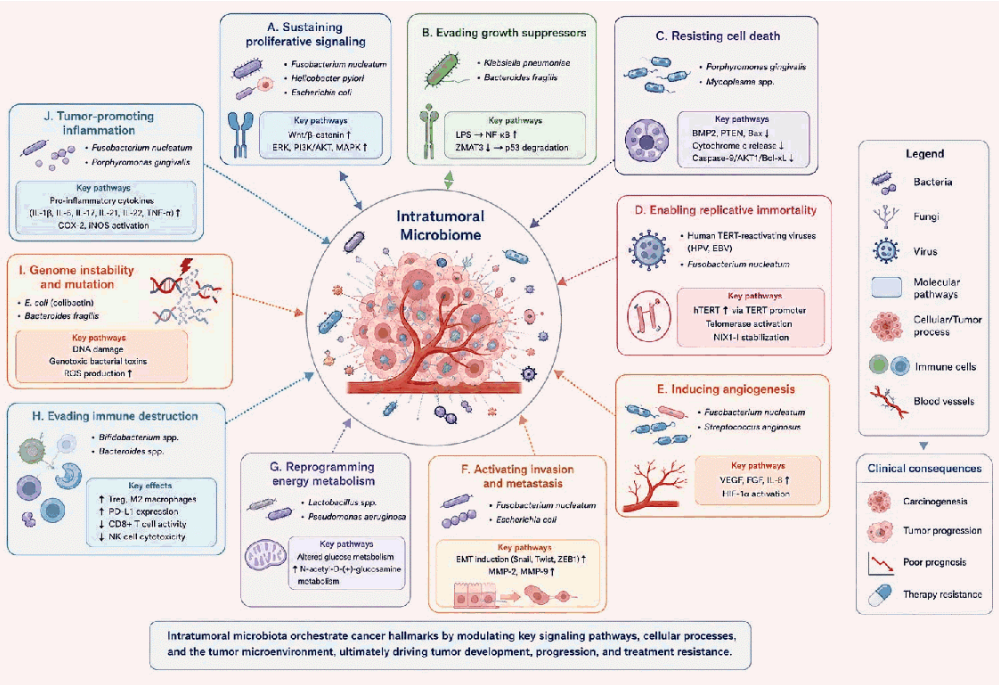
Importantly, such a precise classification serves as a basis for examining the multifaceted impact of the intratumoral microbiome on the hallmarks of cancer. In this context, the microbiome can be defined as a conductor that coordinates tumorigenesis through interactions with microbes and the control of cancer hallmarks. By using hallmark characteristics as the primary goal of manipulation by microbes, researchers can discover details about how microorganisms inhabiting tumors function as multidimensional cancer regulators. The investigation of cancer hallmarks becomes the means to assess how a certain community of microbes or their effectors affects tumors in terms of promotion and development through various means of regulation. These findings indicate that tumor promotion, immune response impairment, metabolic reprogramming, metastasis, and other mechanisms of carcinogenesis can be assessed on the basis of cancer hallmarks (10, 11).

Hallmark-1: maintaining proliferative signaling

Autonomous growth regulation through the activation of proliferation signaling pathways is another critical characteristic feature of cancer cells (12). As a result, cancer cells are able to proliferate without the help of mitogenic stimuli such as EGF and its receptor (EGFR). Malignant bronchial epithelial cell lines were exposed to Streptococcus, Prevotella, and Veillonella in a study by Tsay et al., which resulted in increased activity of the PI3K and ERK signaling pathways that stimulated the growth of cancer cells (13). Growth, proliferation, metabolism, motility, and secretion are only a few of the physiological processes in which members of the PI3K group are involved (13). Importantly, several MAMPs and microbial metabolites can directly cause tumor cells to proliferate (Figure 3A).

As an example, the LPS of gram-negative bacteria stimulates TLR4-NF-κB/MAPK signaling in cancerous cells, resulting in cancer cell proliferation. Metabolites produced by microorganisms have also been shown to promote tumorigenesis. In particular, SCFAs, including acetate and propionate, trigger GPCR-proliferative signaling in cancerous cells (15). In addition, enterotoxigenic Bacteroides fragilis is involved in the process of tumorigenesis through the secretion of a metalloprotease referred to as Bacteroides fragilis toxin (BFT). The Bacteroides fragilis toxin leads to the degradation of E-cadherin in colonic epithelial cells, resulting in the nuclear translocation of the oncoprotein β-catenin. Once nuclear translocation is initiated, β-catenin is involved in transcription and results in hyperproliferation in epithelial cells (16).

The β-catenin pathway is another oncogenic signaling pathway that plays a vital role in tumor formation through the activation of the transcriptional regulation of genes responsible for cell proliferation, differentiation, cell death, and cell migration (17). The causative agent of gastric cancer, Helicobacter pylori, uses the cytotoxin-associated gene A (CagA) protein to trigger cancerous growth. In this context, Once translocated into host cells, CagA dysregulates and activates β-catenin signaling pathways, contributing to oncogenic transformation (18). AvrA produced by Salmonella promotes tumor development by activating downstream targets and the β-catenin signaling pathway (e.g., c-Myc and cyclin D1) (19).



Intratumoral microbiota orchestrate cancer hallmarks by modulating key signaling pathways, cellular processes, and the tumor microenvironment, ultimately driving tumor development, progression, and treatment resistance.

Figure 3: Conceptual overview of the interactions between the intratumoral microbiome and the hallmarks of cancer. The labeled sections represent the following biological processes: (A) proliferative signaling, (B) growth suppressor evasion, (C) resistance to cell death, (D) replicative immortality, (E) angiogenesis, (F) invasion and metastasis, (G) metabolic reprogramming, (H) immune evasion, (I) genomic instability, and (J) inflammation-associated tumorigenesis.

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Hallmark-2: Avoiding growth inhibitors

In addition to being able to generate and maintain growth stimulatory signals, cancer cells have developed ways to escape highly efficient processes that inhibit proliferation (12). Among such processes, many can be attributed to the action of tumor suppressors. The tumor suppressor p53 plays a very important role in the inhibition of tumor growth through various mechanisms. Acting as a transcription factor, p53 acts as a regulator of the transcription of several targets associated with the regulation of cell cycle control, programmed cell death, and genomic maintenance pathways (20, 21). Among the molecules involved in p53 signaling, ZMAT3 has been identified as a key regulator of RNA processing and cellular homeostasis and plays important roles in tumor suppression (22). ZMAT3 functions as an RNA-binding protein that supports the maintenance of p53 mRNA stability. Recent findings indicate that Klebsiella pneumoniae-derived lipopolysaccharides trigger NF-κB activation, which suppresses ZMAT3 expression and ultimately compromises p53 transcript stability. (23) (Figure 3B).

Hallmark-3: preventing cell death

During the course of cancer progression, cancer cells evolve multiple ways to escape or dampen the process of apoptosis, which is a natural safeguard against tumorigenesis (24). P. gingivalis produces NDPK, which phosphorylates HSP27, reducing cytochrome c release and caspase-9 activity and preventing apoptosis (25). Moreover, Mycoplasmas increases BMP2 expression, promotes tumorigenicity and cellular transformation, and stimulates cell proliferation and migration while simultaneously reducing apoptosis (26). In contrast, E. coli Nissle 1917 (EcN), a probiotic microorganism, acts as an anticancer agent in colon carcinoma by promoting apoptotic cell death through the suppression of AKT1 and Bcl-xL signaling and the activation of PTEN and Bax, leading to a reduction in cancer cell proliferation (27) (Figure 3C).

Hallmark-4: making replicative immortality possible

Cancer cells can dedifferentiate back to a stem-cell-like state, which enables them to proliferate infinitely and adapt their metabolism, thus ensuring survival under unfavorable environmental conditions (12). An improper expression of telomerase is considered one of the essential factors responsible for the induction of this characteristic phenotype. Typically, telomeres diminish as somatic cells undergo continuous replication, eventually triggering cell cycle arrest and senescence (28). However, when activated in all cancers caused by HPV infection, telomerase prolongs telomere DNA sequences, blocking apoptosis, senescence, and cell crisis (see Figure 3D). In cancer cells overexpressing the high-risk HPV E6 gene, elevated expression of NFX1-123 may alter cellular proliferative behavior and eventually upregulate hTERT gene expression and telomerase activity. Telomerase-dependent cell immortalization might be among the principal steps in the development of HPV-induced malignancies (29).

Hallmark-5: angiogenesis induction

Angiogenesis is a fundamental process involved in tissue remodeling and tumor expansion in the process of tumor formation, providing necessary nutrients that facilitate the continuous growth and proliferation of tumors (30). Although it is yet to be conclusively proven that bacteria are the cause of angiogenesis within tumors, it is clear that bacteria increase inflammatory activity in the tumor microenvironment, thereby stimulating the production of proangiogenic and chemotactic cytokines and recruiting immune cells through a similar mechanism (Figure 3E). Recent studies have indicated that SCFAs produced by the microbiota influence the process of angiogenesis. One such SCFA is butyrate.

Interestingly, reduced sodium butyrate levels have been linked to increased angiogenesis (31). Kuhn et al. reported that Bacteroides bacteria help maintain intestinal barrier function by activating the production of interleukin-6 (IL-6) from intraepithelial lymphocytes. While low IL-6 levels are usually harmless and may be helpful for mucosal homeostasis, elevated IL-6 concentrations may stimulate oncogenic pathways associated with tumor progression by increasing cell growth, angiogenesis, and invasion while simultaneously inhibiting cell death (32). In recent years, the involvement of TANs in tumor development, angiogenesis, and antitumor immunity has attracted much attention (33).

Experimental evidence revealed that the level of TANs in tumors isolated from mice infected with F. nucleatum was 13.4-fold greater than that in tumors from mice that had not been infected with the bacteria. Furthermore, the number of CD11b+ myeloid cells markedly increased by 3.2-fold (34). CD11b-positive myeloid cell subsets, including macrophages, dendritic cells, and granulocytes, have emerged as key components involved in promoting tumor growth and angiogenesis (35). With respect to gastric cancer, Lactobacillus may activate tumor angiogenesis within the TME through the production of large quantities of N-nitroso compounds (36).

Hallmark-6: initiating metastases and invasion

Epithelial-mesenchymal transition (EMT), an important developmental supervisory mechanism, has been shown to play a critical role in cancer metastasis (37). The CagA protein is among the important virulence factors responsible for the pathogenesis of Helicobacter pylori (38, 39). It has been proven that overexpression of CagA leads to the activation of miR-543, which is a target of SIRT1, an important deacetylase. As a result of the interaction between SIRT1 and miR-543, autophagy can be inhibited by miR-543, leading to increased EMT, which enhances the migration and invasion of gastric cancer cells (40). E-cadherin downregulation has been identified as a critical step in triggering EMT (41). For instance, it has been confirmed that the virulence factor of Fusobacterium adhesin A (FadA) is involved in binding to E-cadherin, promoting adherence and invasion by Fusobacterium (42).

In addition, downregulated expression of the KCNJ11 protein causes upregulation of the Gal-GalNAc carbohydrate structure located on colorectal cancer cell membranes, which makes it possible for it to interact with Fap2 proteins in F. nucleatum to promote adhesion and invasion processes and facilitate the development and onset of colorectal cancer (43). EMT increases the invasiveness and metastatic potential of cells. Methyltransferase3 protein is positively related to tumor proliferation, the EMT process, DNA repair, and invasive potential. Clostridium butyricum downregulates METTL3 expression through an increase in the expression of GPR3 G protein-coupled receptor 3 (G protein-coupled receptor 3), which leads to a decrease in the expression of vimentin and VEGFR2 vascular endothelial growth factor receptor 2 (vascular endothelial growth factor receptor 2). Consequently, Clostridium butyricum decreases the EMT process and VM, thus reducing the metastatic potential of tumor cells (44).

Moreover, studies have shown that CPE can be used as a therapeutic target to treat OSCC. On the one hand, CPE promotes the proliferation, migration, and invasion of OSCC cells through the induction of nuclear translocation of CLDN4, inhibits YAP1 phosphorylation, increases YAP1 expression, and promotes cancer growth and EMT, leading to cancer metastasis. Therefore, targeting CPE has emerged as an effective method for OSCC treatment (45). Fusobacterium nucleatum triggers the activation of the TLR4/AKT signaling pathway, decreases the expression of Keap1, increases the expression of NRF2, and promotes the transcription of CYP2J2, which results in increased levels of 12,13-EpOME. As a result, the EMT and metastasis of CRC cells are stimulated. Hence, the activation of this signaling pathway can be used as a potential biomarker for CRC patients harboring F. nucleatum infection (46).

Toxins generated by Bacteroides fragilis in the tumor microenvironment have been shown to cause a migratory and invasive phenotype in human breast cancer cell lines and to increase the expression of EMT markers, including the transcription factors Twist and Slug. By colonizing the mammary ducts, Bacteroides fragilis can promote the metastasis of tumor cells to other organs. (47). Recently, it was discovered that intratumoral microbes living within breast cancer cells encourage metastatic colonization. This occurs because these microbes influence the cytoskeleton of host cells and help tumors survive in the fluid shear conditions of circulation (48) (Figure 3F).

Hallmark-7: Microbiome-Associated Metabolic Rewiring

One of the defining characteristics of malignant cells is their ability to remodel metabolic pathways in response to environmental and energetic demands. These adaptations support continued growth and survival under unfavorable conditions (10). The role played by microbes within the tumor in relation to this adaptive mechanism has been recognized through alterations in the glycolytic rate, nutrient accessibility and metabolite-mediated communication within tumor cells (Figure 3G). Different bacterial groups have been observed in various tumors, with their presence correlated with metabolic characteristics and interactions between the tumor microenvironment and the immune system (5, 49). For example, the abundance of the bacterium Pseudomonas koreensis is correlated with N-acetyl-D-glucosamine and negatively correlated with citrulline (49).

In a different investigation carried out by Zheng et al., F. nucleatum caused glycolytic activity in colorectal cancer through increased ANGPTL4 expression (50). Increased expression of ANGPTL4, in turn, enables colonization by promoting the expression of GLUT1 and glucose uptake. Moreover, in addition to upregulating ANGPTL4 expression, F. nucleatum activates the transcription of the long noncoding RNA ENO1-IT1 via the transcription factor SP1. The increased expression of ENO1-IT1 promotes the recruitment of the histone acetyltransferase enzyme KAT7, which causes changes in the histone modifications of targeted genes, allowing increased glycolysis and carcinogenesis in colorectal cancer (51). F. nucleatum promotes the activation of the GalNAc–autophagy–TBC1D5 pathway, leading to elevated GLUT1 expression and lactate production, which contributes to the development and progression of oral squamous cell carcinoma (52). In vitro experiments have shown that the oncogenic expression of MCVs increases the expression of genes related to glycolysis, such as the monocarboxylate transporter SLC16A1 (MCT1) (53).

Hallmark-8: avoiding immune destruction

Mechanisms by which solid tumors escape immune surveillance have been developed, indicating that solid tumors escape from T cells, B cells, macrophages, and natural killer (NK) cells. In addition, intratumoral microbes assist solid tumors in evading immune surveillance by preventing the infiltration of immune cells into tumors, which ultimately affects the development and growth of tumors (54) (Figure 3H).

The presence of Fusobacterium nucleatum in tumors inhibits the cytolytic properties of NK cells and TILs by virtue of the association between Fap2 proteins expressed on the surface of the bacterium and the human inhibitory receptor TIGIT and thus glycolytic activity in colorectal cancer through increased ANGPTL4 expression (55). The level of Fusobacterium nucleatum colonization in colorectal carcinoma tissues is inversely associated with the number of CD3+ T cells. Decreased expression of CD3+ T cells in tumors can result in decreased surveillance immunity and impaired antitumor immunity, hence accelerating tumorigenesis (55). However, recent research has shown that F. nucleatum can enhance PD-1 blockade therapy in microsatellite-stable colorectal cancer (56).

The dysbiosis of enterotoxigenic Bacteroides fragilis (ETBF) promotes TAM polarization into M2 macrophages and helps colorectal cancer cells evade the immune system in mice. The colonization of ETBF in germ-free mouse models triggers the p-STAT3 signaling pathway, which promotes M2 macrophage polarization to induce chronic inflammation and immunosuppression, leading to the development of colorectal cancer (57).

In addition, the commensal bacteria Peptostreptococcus sp. in the uterine microbiome can facilitate the induction of IDO1 gene expression in response to IAA secretion. The induction of IL-10 expression by IAA secretion from macrophages in the endometrium enhances IFN-γ secretion by CD8+ T cells. Elevated IFN-γ secretion induces increased IDO1 expression in EC cells, promoting Trp catabolism to increase the Kyn content. The loss of Trp and increased Kyn levels stimulate the differentiation of Tregs, suppressing the proliferation and activity of CD8+ T cells and promoting the immune-tolerant microenvironment in EC tumors (56).

Bacteroides that express bile salt hydrolase (BSH) have been shown to facilitate the development of colorectal cancer because of their ability to increase the concentration of unconjugated bile acids, which triggers the activation of the β-catenin/CCL28 pathway, ultimately leading to the recruitment of regulatory T cells to the tumor microenvironment (52). Overall, on the basis of the current literature, microbial effects on the tumor microenvironment primarily occur via immune tolerance induction and T-cell exhaustion, thus allowing immune evasion by tumor cells.

Interestingly, other studies have reported that intratumor bacteria can activate immunity in patients and induce antitumor responses (58, 59, 60). For example, Bifidobacterium residing in the gut can colonize tumors and trigger T-cell-mediated tumor rejection through the induction of the STING/IFN-I pathway in DCs infiltrating tumors (58).

Hallmark-9: mutation and instability of the genome

Tumorigenesis is a multistep process driven by the progressive accumulation of genetic alterations within malignant cells (61). These genomic abnormalities contribute to DNA damage and genomic instability, thereby promoting cancer development (Figure 3I). In gastric epithelial cells, Helicobacter pylori infection is associated with the induction of DNA double-strand breaks and increased expression of the cytidine deaminase (CDA) enzyme. It can cause genetic mutations and contribute to the development of gastric cancer via dysplasia (62). Metabolic products, including indoleamine from Morganella organisms, cause genetic mutations and leaky intestinal walls, increasing the risk of developing colorectal cancer (63). Campylobacter sp. secretes cytolethal distending toxins (CDTs), which facilitate DNA double-strand breakages and contribute to the onset of colorectal cancer (64).

Human T-cell leukemia virus type 1 (HTLV-1), which is a retrovirus, may impair essential proteins involved in DNA double-strand break repair, including E3 ubiquitin ligase and ubiquitin conjugases (ring finger protein 8), through the viral protein Tax, resulting in genomic instability and the development of oncogenic mutations (65). The bacterium Fusobacterium nucleatum can cause DNA damage and stimulate cell proliferation via activation of the E-cadherin/β-catenin pathway in a manner dependent on FadA and Chk2 gene expression (66). In addition, the latest reports have shown that KRAS mutations are required for ETBF colonization within colorectal cancer tissues and that the miR-3655/SURF6/IRF7/IFN-β signaling cascade is the most important regulatory network.

This is the first mechanistic proof for such regulation (67). E. coli strains possessing the virulence island pks produce a series of enzymes responsible for colibactin biosynthesis, which leads to DNA alkylation of adenine bases and double-strand breakage in cultivated cells (68). TP53 is the most frequently altered gene in lung cancers (69). In cases in which the TP53 gene is mutated in squamous cell carcinomas, an increase in the presence of Acidovorax bacteria occurs, suggesting that the association between microbial dysbiosis and TP53 mutation may be a causative factor for lung tumors (70).

Hallmark-10: inflammation that promotes tumors

Persistent inflammation is widely regarded as an enabling condition for tumor development. Accumulating evidence suggests that microorganisms residing within tumors can shape local inflammatory responses by influencing cytokine networks and immune-related signaling pathways. Through these mechanisms, microbial communities may contribute to a microenvironment that favors cancer progression (Figure 3J). As a central mediator of inflammation-associated cancer, NF-κB regulates numerous genes involved in tumor development and immune modulation (72). Hoste et al. demonstrated that the skin microbiota can influence inflammatory responses in skin cancer through TLR5-dependent signaling mechanisms (73).

Furthermore, the Fusarium-induced activation of the TLR4/MYD88/NF-κB signaling cascade is associated with elevated miR-21 expression in tumor cells. Increased miR-21 levels suppress Ras protein activator-like 1 (RASA1), resulting in the activation of intrinsic RAS signaling pathways and increased expression of genes involved in cellular proliferation and growth. In addition, upregulation of miR-21 expression promotes the production of inflammatory mediators, including IL-17F, IL-21, IL-22, and MIP-3A, which further support tumor progression. Additional evidence for inflammation-driven carcinogenesis was provided by Goodwin et al., who reported that Bacteroides fragilis toxin (BFT) induces the expression of spermine oxidase (SMO) (74). Increased SMO activity promotes the generation of reactive oxygen species (ROS), leading to DNA damage, enhanced epithelial cell proliferation, and the development of colorectal cancer. Because bacterial-induced ROS production is largely mediated by SMO, this enzyme has been proposed as a potential target for cancer chemoprevention (74). Similarly, mice predisposed to colorectal cancer and colonized with enterotoxigenic Bacteroides fragilis exhibit elevated IL-17 levels, increased epithelial DNA damage, accelerated tumor growth, and reduced survival, further supporting the role of inflammation in tumor development (75). In liver-associated tissues, higher levels of SELE, an adhesion molecule implicated in inflammation, have been observed in normal adjacent tissues than in liver tumors. Furthermore, an inverse relationship between Malassezia colonization and SELE expression has recently been reported, suggesting that intratumoral Malassezia may contribute to the regulation of local inflammation

Microbiome–Host Genome Interactions:

Emerging evidence indicates that the intratumoral microbiome not only shapes inflammatory and immune processes but also directly interacts with host regulatory and epigenetic networks. This interaction between the microbiome and the host genome appears to drive cancer development and pathogenesis by modifying genomic stability and signaling pathways. Importantly, this relationship appears to be bidirectional: host genetic alterations can influence microbial colonization, whereas microbial communities may shape tumor development and molecular heterogeneity (43, 64).

Recent studies have shown associations between specific microbial species and recurrent genetic alterations associated with cancer. In colorectal cancer, mutations in the KRAS gene have been shown to promote tumor colonization by enterotoxin-producing Bacteroides fragilis through the regulation of the miR-3655/SURF6/IRF7/IFN-β signaling axis, highlighting a direct interaction between the mutation status of the host and the microbial composition (49, 67). Similarly, genomic profiling studies have revealed associations between tumor-associated microbial communities and specific genomic alterations in the host, indicating that tumor genetics may partly determine the selection of the microbial environment within the tumor microenvironment (43, 64).

Microorganisms can also participate in genomic instability by producing genotoxic metabolites and activating DNA damage pathways, since symbiotic bacteria isolated from patients with inflammatory bowel disease have been reported to produce genotoxic compounds that can induce DNA damage (63). Similarly, the bacteria Fusobacterium nucleatum has been shown to promote the development of colon and rectal cancer through DNA damage-associated signaling, including increased expression of checkpoint kinase 2 (CHK2), which links microbial colonization to genomic instability and tumor development (66). These findings are of particular interest because genome instability is a hallmark of cancer (61).

Beyond genetic mutations, the microbiome within the tumor may influence tumor biology via epigenetic regulation, as microbial metabolites have been shown to be involved in the regulation of DNA methylation, histone modifications, and noncoding RNA expression. For example, indole-3-lactic acid extracted from Lactobacillus plantarum has been shown to regulate antitumor immunity through epigenetic mechanisms affecting CD8+ T-cell function (44, 60). In addition, Fusobacterium nucleatum can promote the formation of colorectal tumors by regulating long noncoding RNA pathways involved in cellular metabolism and cancer signaling (51). Taken together, these observations suggest that microbial communities may affect cancer development through genetic and epigenetic mechanisms.

In addition, microbial imbalance has been reported to be associated with host genetic alterations in lung cancer. Increased numbers of specific bacterial species have been associated with mutations in the TP53 gene, supporting the possibility that the composition of the microbiome and the interactions between the tumor and the microbes might be influenced by the host genetic background (70). While the underlying mechanisms are not fully understood, increasing evidence suggests that the interaction of the microbiome with the host genome is an important component of tumor biology and may provide new opportunities for the discovery of biomarkers and precision oncology.

Intratumoral Virome and Cancer

Although bacteria are the most studied component of the tumor microbiome, many recent studies have pointed to the role of viruses within tumors as important drivers of cancer initiation, progression, and response. This viral community comprises classical oncogenic viruses as well as other viruses that constitute the tumor microbiome, and their role in carcinogenesis is demonstrated through genomics, chronic inflammation, and immune modulation. Scientific evidence has shown that many viruses are carcinogenic agents in humans. Human papillomavirus (HPV) is strongly associated with cervical cancer, as well as some head and neck cancers, because of its role in cancer-causing activities via the E6 and E7 proteins, which disrupt the TP53 and RB molecular pathways involved in tumor suppression (104). For example, hepatitis B virus (HBV) and hepatitis C virus (HCV) are major agents that cause hepatocellular carcinoma through persistent inflammation and genomic instability, as well as disruption of the body's cellular information network (105). Other oncogenic viruses include human T-lymphoblastic leukemia virus type 1 (HTLV-1), which causes leukemia or T-lymphoblastoma in adults, and other viruses (106, 107). In addition to these well-known oncogenic viruses, recent genomic sequencing studies have revealed a diverse array of viruses in cancer tissues. Although the roles of many of these viral groups are not fully understood, according to the latest scientific data, these viruses may play a role in regulating cellular immune functions, inflammatory signaling, and interactions between cancer cells and other microorganisms in the microscopic environment of tumors (77, 99). Attention should be given to the distinction between classical oncogenic viruses and nononcogenic viral groups that may indirectly contribute to tumor biology by modulating host immunity and interacting with the bacterial and fungal components of the tumor microbiome.

In general, current evidence suggests that tumor viruses are key yet understudied components of the tumor ecosystem. Further research is needed to elucidate the mechanisms by which viral communities interact with cancer cells, host genes, and other microbial communities to influence cancer characteristics and treatment outcomes.

Other signs

Four more criteria have been added to cancer hallmarks in 2022 by Hanahan, specifically "polymorphic microbiomes," "nonmutagenic epigenetic reprogramming," "unlocking phenotypic plasticity," and "senescent cells". (10). Specific microbiome signatures were identified in tissues and blood from several cancers, including colorectal, breast, ovarian, lung, gastric, bladder, prostate, head and neck, and pancreatic cancers (5, 76)

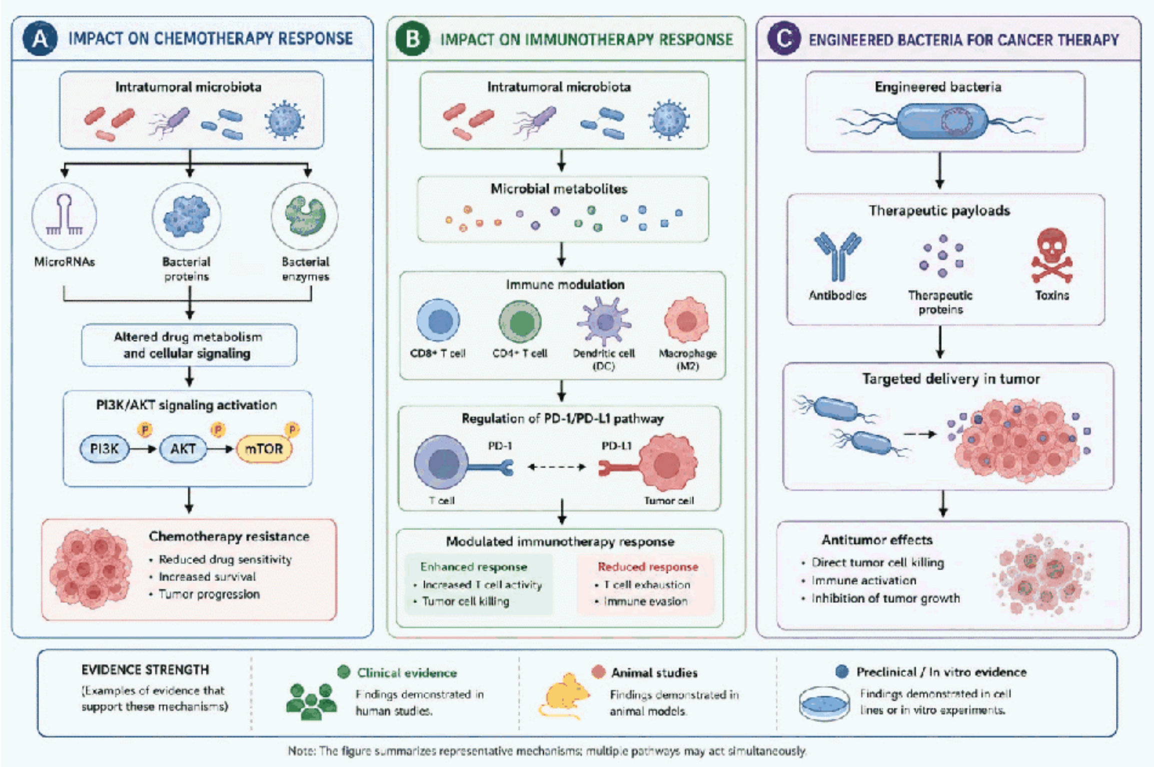
The signatures were also used to differentiate between normal individuals and cancer patients, thus demonstrating their diagnostic potential. In a recent pancancer study, the occurrence of fungi linked to cancer in 17,401 samples from 35 different cancer cases was investigated. Although fungi and their DNA can be detected in small quantities in some of the most prevalent cancers in humans, they show distinct community structures among different cancers. Different fungal strains, along with their cellular structures, are strongly correlated with certain cancer types (77).

In summary, tumor microbiomes consist mostly of bacteria, along with an insignificant number of fungi. The microbial population in the normal tissues surrounding the tumor is almost identical to that found in the tumor. Several microorganisms are found in various tumors, but their numbers vary from one type of cancer to another (78). The gut microbiota is important for the survival of the host because it is involved in diverse functions, such as food digestion, defense against pathogens, the production of bioactive molecules, and communication with the brain (79).

Disruption of these two-way microbial-host interactions can cause dysbiosis, which in turn can cause aging and age-related diseases such as cancer (80). Furthermore, investigations have shown the relationship between the presence of microorganisms and the formation of tumors through the establishment of epigenetic landscapes, such as those involving histone modifications, ncRNA regulation, RNA methylation, and DNA methylation (51, 81). Studies on the impact of microbiomes on achieving phenotypic plasticity are still limited. Having better knowledge about the participation of tumor-inhabiting microbes in this phenomenon will aid in understanding the intricacies of cancer.

Intratumoral microbiome application

Owing to advances in the field of tumor microbiome studies, in addition to the regulatory role played by microorganisms in tumor development, microbes can be used as potential targets for cancer treatments. Recently, the involvement of microbes in different types of therapies, including chemotherapy and immunotherapy, has attracted much interest owing to their role in immune response modulation and overcoming resistance to treatment. In addition, the use of genetically engineered microbes has opened up a range of opportunities to explore personalized cancer treatment (Figure 4) (8, 9). It is clear, therefore, that the tumor microbiome is not only gaining significance in the domain of cancer biology but also holds promise for use in cancer treatment.



Note: The figure summarizes representative mechanisms; multiple pathways may act simultaneously.

Figure 4: Opportunities for intratumoral microbiome application. The intratumoral microbiome can (A) influence the effectiveness of chemotherapy through enzyme metabolism and signaling, (B) influence immune checkpoint mechanisms, and (C) act as a vector for therapeutic cargo.

* Created by the authors using Canva Pro. Conceptually derived from published studies investigating microbiome-based therapeutic approaches in cancer, including chemotherapy modulation, immunotherapy enhancement, engineered bacterial therapies and microbiome-targeted interventions. This figure represents an original illustration synthesized from the literature and was not directly adapted or reproduced from any previously published figure.

Effects of the intratumoral microbiome on chemotherapy efficacy

Resistance is one of the primary reasons for the failure of chemotherapy against cancer. It has become increasingly apparent that tumor-associated bacteria play an important role in contributing to chemotherapy resistance because of the metabolism of chemotherapy agents. Bacterial DNA was identified in 76% of pancreatic cancer patients, in which γ-proteobacteria were the predominant bacterial species. One form of cytidine deaminase (CDD), which can modify the drug gemcitabine to make it chemically inert, has been discovered in these bacteria (82).

Other investigations have shown that there is an increase in the presence of Fusobacterium nucleatum in the tissues of patients who experience chemotherapy relapse. They stimulate the activation of the autophagy process through a reduction in the expression of miR-18a and miR-4802; in turn, these activities promote chemotherapy resistance in this disease (83). According to Lehouritis et al., the presence of Escherichia coli can potentiate the effects of tegafur while weakening the effects of cytarabine, gemcitabine, and etoposide phosphate. In an experiment conducted on mice with colon cancer tumors, Lehouritis et al. reported that, in comparison with the gemcitabine alone group, the gemcitabine plus bacteria group exhibited a marked increase in tumor size and a low survival rate.

Other studies have demonstrated that the occurrence of dysbiosis in the microbiota leads to increased resistance to chemotherapy among tumors (84, 85, 86). For instance, F. nucleatum affects the endogenous expression of LC3 and ATG7 proteins, hence contributing to autophagy and resistance to drugs such as 5-fluorouracil, cisplatin, and docetaxel (87). Additionally, gut microbiota-derived butyrate facilitates the acquisition of resistance to chemotherapy for colon cancers by activating the PI3K/AKT pathway (88).

Research has also revealed bacteria that take part in the metabolism of anthracycline drugs. Specifically, Streptomyces WAC04685 and Raoultella planticola are known to degrade doxorubicin via deglycosylation (89, 90). There is potential to develop new approaches to counter resistance by using a combination of antitumor therapy and the intratumoral microbiome. However, considerable disparity remains between the preclinical research phase and its actual implementation in clinical settings because of regulatory issues. Therefore, resolving these problems and conducting well-designed clinical studies are important in this area.

Effects of the intratumoral microbiome on immunotherapy efficacy

In the past few years, immunotherapy has emerged as an essential element of cancer therapy. Agents such as PD-1 inhibitors that interfere with the interaction between PD-1 and its ligand have been found to effectively enhance T-cell-mediated immune cytotoxicity. The lack of functional capacity among effector T cells, especially CD8+ T cells, is responsible for the ineffectiveness of this therapeutic regimen in most patients (91). Recent studies have demonstrated that the tumor microbiome significantly influences ICI responsiveness by regulating CD8+ T-cell activity, T-cell priming, cytokine signaling, and the immunological microenvironment. (92).

For instance, 16S rRNA gene sequencing revealed that Bifidobacterium is involved in regulating tumor development. The inhibition of DC activity in tumors by Bifidobacterium results in an increase in the number of CD8+ T cells, thus enhancing the ability of anti-PD-L1 to regulate tumor development (93). Streptococcus mitis plays a key role in hindering the progression of gastric cancer by preventing M2 macrophages from infiltrating tumors and altering the composition of the tumor microenvironment (94).

The polysaccharides of Malassezia cell walls have been shown to trigger the activation of the host complement system through MBL activity, contributing to the development of pancreatic cancer. On the other hand, the profusion of anaerobic bacteria (Bacteroides, Lactobacillus, and Peptostreptococcus) leads to decreased numbers of CD4+, CD8+, and CD45RO+ infiltrating tumor cells and poor outcomes in patients with pancreatic cancer (95). Microbial metabolic products can also act as functionally important regulators in T-cell regulation. Butyrate has been demonstrated to increase CD8+ T-cell sensitivity to IL-12 and IFN-γ production by upregulating ID2 expression (96). Recently, the metabolism of dietary tryptophan by Lactobacillus reuteri has been shown to produce AhR agonists, such as indole-3-aldehyde, leading to the activation of AhR signaling in tumor-infiltrating CD8+ T cells and improving IFN-γ production and the antitumor immune response (97). Additionally, recent studies have explored and confirmed that the intratumoral microbiota is a significant predictor of the efficacy of neoadjuvant immunotherapy as part of a chemoimmunotherapy regimen in early-stage triple-negative breast cancer (TNBC) (98). This finding highlights the importance of the microbiome in the efficiency of immunotherapy by some particular bacterial species enhancing the therapeutic effect. Nonetheless, the practical use of the intratumoral microbiota in immunotherapy still faces serious obstacles, including personal variation and technical constraints. Resolving such issues requires more sophisticated technologies and standardized methodologies to assess the true contribution of microbiota manipulation to the efficiency of immunotherapy.

Oncological effects of engineered bacteria:

Gene editing has opened up new possibilities regarding new techniques that can be used to treat cancers through genetic engineering. Genetic engineering is more advantageous than other conventional forms of therapy in the treatment of cancer. Genetically modified bacteria can produce certain products or cause certain reactions that prevent the growth of tumors. Additionally, genetically modified bacteria can act as carriers that deliver toxins, immune activators, and other substances (99).

A nonpathogenic E. coli strain producing CD47 nanobodies was created by Chowdhury et al. The produced nanobodies self-aggregate and are spontaneously liberated from inside the body. They are bound to the CD47 protein found on the surface of cancer cells. As a result, the ability of these cancer cells to avoid immune responses is decreased; therefore, they become more vulnerable to immune system attack (100). A system based on a probiotic designed by Gurbatri employs a robust lysis method to regulate the secretion of PD-L1 and CTLA-4 nanobodies in tumors, which resulted in improved activation of T cells in mice, considerable inhibition of the development of lymphomas, induction of distant effects, and increased life span (101). Systemic delivery of TNF-α, a strong anticancer drug, causes significant toxic effects. In this way, TNF-α is generated in CT26 tumors in mice by E. coli strain MG1655, a tumor-targeting vector (102).

In addition, a genetically modified Salmonella Typhimurium strain has been designed that can generate Vibrio vulnificus flagellin B only in tumors in mice. This triggers M1-type macrophages and reduces the activity of M2-type macrophages by stimulating the TLR4 pathway (103). However, many obstacles hinder the use of genetically modified bacteria for cancer treatment, such as problems with their toxicity, stability, unlimited growth, and best way to administer them. Genetically modified bacteria appear to be a very promising future for cancer treatment.

To facilitate interpretation of the available literature, microorganisms were categorized according to the predominant level of supporting evidence (in vitro, animal, clinical, or combined evidence), and the intratumoral microorganisms that have been identified to be involved in cancer development are listed in Table 1 along with the cancers they have been linked with and the supporting evidence.

Table 1: Representative intratumoral microorganisms associated with cancer, their proposed mechanisms, molecular pathways, and levels of supporting evidence.

Evidence Level	Molecular Pathway	Key Mechanism	Cancer Type	Microorganism
Animal + Clinical	Wnt/β-catenin, TLR٤/NF-κB, EMT pathways	Promotes proliferation, metastasis, immune evasion	Colorectal, Breast	*Fusobacterium nucleatum*
Clinical	CagA → β-catenin, NF-κB activation	Induces inflammation, DNA damage, oncogenic signaling	Gastric cancer	*Helicobacter pylori*
Animal	Akt/STAT3, PD-L1 upregulation	Immune suppression, tumor progression	Oral, Gastrointestinal	*Porphyromonas gingivalis*
Animal	NF -κB, STAT3 activation	Chronic inflammation, epithelial damage	Oral cancer	*Candida albicans*
Animal + Clinical	Complement activation, PD-L1 modulation	Immune evasion, tumor progression	Pancreatic, Breast	*Malassezia* spp.
Clinical	Colibactin → DNA crosslinking	DNA damage and mutagenesis	Colorectal cancer	*pks*$^{+}$ *Escherichia coli*
Animal + Clinical	β-catenin signaling, inflammation	Toxin-mediated carcinogenesis	Colorectal cancer	*Bacteroides fragilis (ETBF)*
In vitro + Animal	β-catenin activation	Enhances tumor initiation	Gastrointestinal	*Salmonella* spp.
Clinical	E6/E7-mediated inhibition of p53 and Rb pathways; hTERT activation	Inactivation of tumor suppressor proteins and induction of cellular immortalization	Cervical cancer, Head and neck cancer	Human papillomavirus (HPV)
Clinical	Persistent inflammatory signaling, DNA damage, and oncogenic pathway dysregulation	Chronic inflammation, genomic instability, and hepatocarcinogenesis	Hepatocellular carcinoma	Hepatitis B virus (HBV)/Hepatitis C virus (HCV)
Clinical	Tax-mediated impairment of DNA repair and oncogenic signaling	Promotes genomic instability and malignant transformation	Adult T-cell leukemia/lymphoma	Human T-cell leukemia virus type 1 (HTLV-1)
Clinical	Viral T-antigen expression and glycolytic pathway activation	Viral integration and metabolic reprogramming associated with tumor development	Merkel cell carcinoma	Merkel cell polyomavirus (MCPyV)

Microbiome and Oncolytic Virotherapy

Oncolytic virus therapy represents an attractive approach to cancer treatment involving either genetically modified or natural viruses that can infect and kill tumor cells, thus inducing an antitumor immune response at the same time. Recently, increasing emphasis has been placed on the possible interactions between the tumor-associated microbiome and oncolytic viruses. It is becoming increasingly clear that microbiomes may play a role in antiviral immunity and hence impact oncolytic virotherapy. Metabolites and molecular patterns produced by the microbiome can shape innate and adaptive immunity, possibly impacting viral replication, immune cell recruitment, and therapy. Alternatively, oncolytic viruses may restructure the tumor microenvironment in such a way that it alters the microbial community structure (8, 80).

The potential of the microbiome in terms of its ability to modulate immunity could also be used in developing synergistic treatment approaches. Microbial activation of dendritic cells, cytotoxic CD8+ T cells, and interferon signaling pathways can improve antitumor immunity and lead to better results in immunotherapy treatments (17, 58, 93). This approach could be helpful for improving virotherapy results. However, even with these encouraging observations, the dynamics of the association between intratumor microbes and oncolytic virotherapy have not yet been well characterized. Existing information in most cases comes from preclinical models, and more research is necessary to elucidate the impact of microbial communities on the survival, efficacy, and safety of oncolytic viruses in humans with cancer.

Limitations and Future Perspectives

Although there have been numerous advances in the understanding of the significance of the microbiota in the growth of tumors, several issues need to be addressed within this research area. Currently, the majority of studies utilize experimental models or animal models, which limits the transferability of their results to humans. Moreover, many findings are based on correlations rather than direct causation of the development of tumors by microbes (8). There are also a number of problems associated with the actual study of microorganisms in tumors, starting from the issue of contamination, which may cause biased findings because of the low mass of microorganisms in some types of tissue. Finally, the lack of uniform protocols in terms of gene sequencing and data analysis has led to great discrepancies across different studies. Additionally, the microbiota shows significant interpersonal variability depending on variables such as the environment, dietary habits, and overall health status. This makes identifying a stable bacterial composition that defines a particular type of cancer quite difficult. Moreover, the dynamic interplay between microbes and the cancer microenvironment remains poorly understood, especially with respect to changes in time course during disease development and therapy. Thus, further advancements in this field necessitate large clinical cohorts, long-term investigations, and the application of sophisticated analytical methods and multidimensional datasets (multiomics). Such an approach will facilitate the faster transition of this knowledge into practice (3, 5).

Therapeutic Consequences and Clinical Translation of the Intratumoral Microbiome

The intratumoral microbiome offers an exciting opportunity for clinical use both as a diagnostic tool and as a therapeutic target. As a diagnostic tool, the presence of specific microbes may serve as noninvasive biomarkers for the early detection of tumors, prognostic value, and responsiveness to therapy, especially given recent developments in gene sequencing and multilevel analyses. The role played by modulating the gut microbiome in the treatment of cancer has been proven, and this finding has shown that the effect may be direct to the efficacy of the anticancer treatment used. This is because some microbes increase or reduce the response of patients to immunotherapy treatments, such as PD-1/PD-L1, by influencing the immune status of the tumor. Different treatments have been suggested, such as probiotics, antibiotics, and FMT. Moreover, gaining knowledge about how the microbiome and medications interact also allows scientists to embark on the path toward the creation of personalized medicine that would use microbiome properties to help select the best medication for each person. Nevertheless, research in this area remains at an early stage and is currently limited by challenges related to safety, standardization, and optimal therapeutic implementation. As a result, practical implementation of such knowledge needs large-scale clinical research in combination with the development of personalized treatment strategies (8, 9).

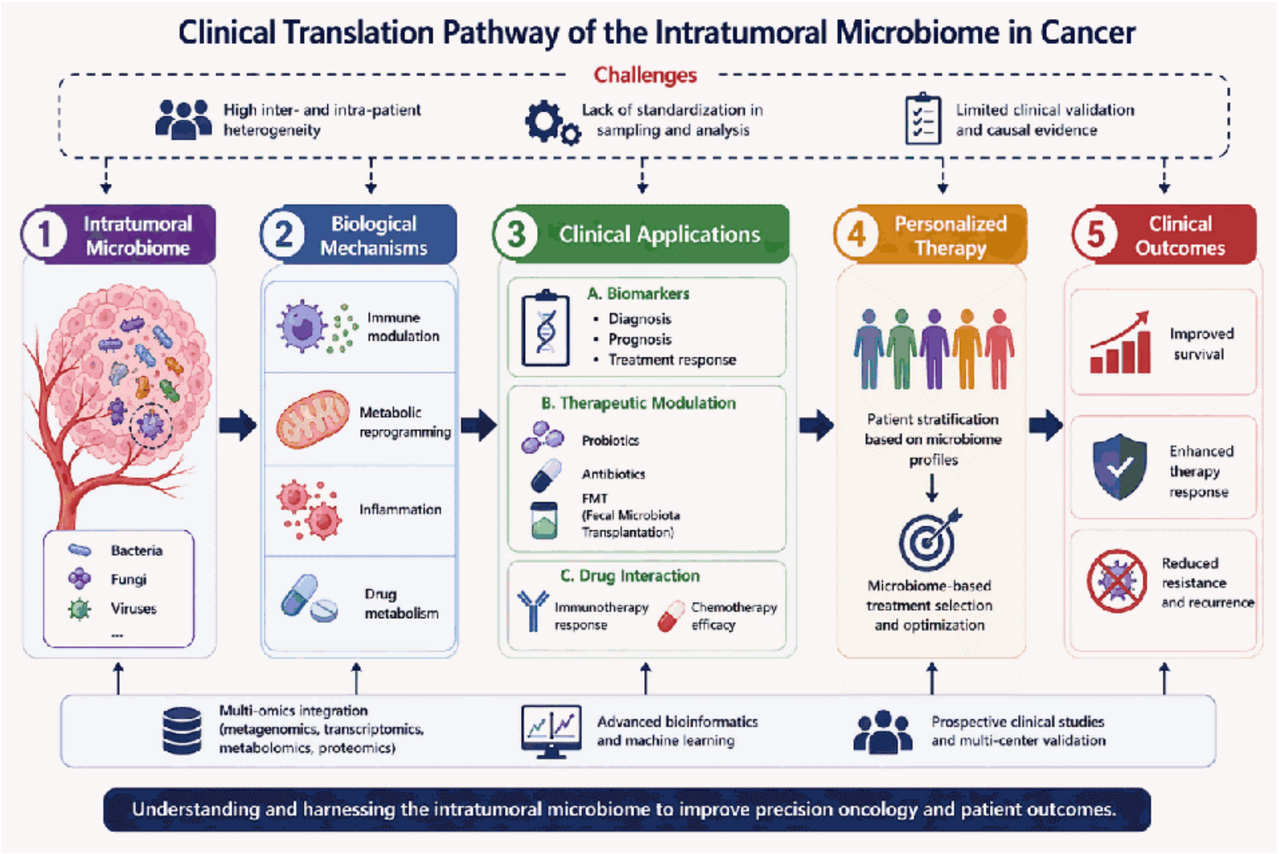


Figure 5: Pathway for the clinical translation of the intratumoral microbiota in oncology, representing how the biology is translated into clinical practices and personalization of treatment options.

* Created by the authors using Canva Pro on the basis of evidence synthesized from published studies discussing the clinical translation of intratumoral microbiome research. This figure is an original illustration and was not directly adapted or reproduced from any previously published figure.

Conclusion

With increasing attention given to studies of the gut microbiome–cancer relationship, the field of study has slowly moved toward the contribution of the tumor microbiome to carcinogenesis and how these effects are treated in cancer patients. Advances in analytical technologies used to investigate gut and intratumoral microbial communities have considerably expanded our understanding of host–microbiome interactions and their relevance to human health. On the other hand, studies of intratumoral microbiome have only been in their infancy. One of the critical points is that the resilience of the immune system is yet another important variable that complicates the role of the microbes studied in tumors. For example, evidence from clinical practices shows that the immune tone of patients is highly susceptible to systemic changes, such as a state of impaired early immune recovery due to malnutrition before surgery among cancer patients (52).

While increasing attention is being given to the microbiota associated with tumors, methodological constraints still constitute one of the key challenges in this area of research. The issue of contamination poses a continuous problem for the examination of low-biomass tumors; even tiny amounts of microorganisms present due to contamination in laboratory solutions, the external environment, or even the researchers themselves could be erroneously identified as endogenous tumor microorganisms, thus affecting the validity of the results (104). Recent studies have re-evaluated microbial signatures identified in cancer tissues, suggesting that a proportion of previously reported intratumoral microbial profiles may have been influenced by contamination artifacts (105).

Moreover, variations caused by sample preparation artifacts, such as different levels of sample preservation procedures, cell lysis methods, or DNA isolation methods, may affect the binding of bacterial DNA, thus hindering comparative study efforts. Modern sequencing techniques have been unable to determine the presence of live bacteria from dead bacteria, which hinders functional analysis of tumor-associated microbes (106). Another problem is the issue of reproducibility. Sample preparation techniques and sequencing platforms can bias the results, causing inconsistencies in tumor microbial compositions in studies conducted using different sequencing machines even when performed in the same laboratory. Spatial resolution through advanced spatial transcriptomic approaches and high-resolution imaging technologies is necessary for improving the reliability and reproducibility of data gathered on the topic.

In addition to solving these issues, understanding the molecular pathways through which bacteria colonize and thrive in the tumor microenvironment and analyzing microbe–tumor interactions affecting tumorigenesis, tumor evolution, and therapeutic effectiveness are critical. Furthermore, translating microbiome interventions from the laboratory into clinical practice necessitates the formulation of standardized procedures and effective biomarkers for assessing the tumor microbiome and forecasting therapeutic results. Additionally, understanding the impact of modifying the intratumoral microbiome on improving current cancer treatments will enable the formulation of synergistic treatments. Solving these crucial obstacles will pave the way for facilitating the clinical translation of tumor microbiome research and accelerating the process of developing microbiome-driven cancer therapies. A deeper understanding of intratumoral microbial ecosystems is expected to provide valuable insights for future cancer research and therapeutic innovation.

Author Declarations

Authors' Contributions

All authors contributed equally to the conception and design of the review. All authors participated in the literature search, data interpretation, manuscript preparation, critical revision of the manuscript, and approval of the final version for publication. All authors read and approved the final manuscript.

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Ethical Approval and Consent to Participate

Not applicable. This study is a narrative review article based exclusively on previously published literature and did not involve human participants, animals, clinical specimens, or patient data. Therefore, ethical approval and informed consent were not required.

Consent for Publication

Not applicable.

Availability of Data and Materials

No new datasets were generated or analyzed during this study. All information discussed in this review was obtained from previously published articles cited in the reference list.

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Competing Interests

The authors declare that they have no competing interests or conflicts of interest regarding the publication of this manuscript.

References

1. Gao, F., Yu, B., Rao, B., Sun, Y., Yu, J., Wang, D., et al. (2022). The effect of the intratumoral microbiome on tumor occurrence, progression, prognosis and treatment. Front. Immunol. 13:1051987. doi: 10.3389/fimmu.2022.1051987.
2. Qu, D., Wang, Y., Xia, Q., Chang, J., Jiang, X., and Zhang, H. (2022). Intratumoral microbiome of human primary liver cancer. Hepatol. Commun. 6, 1741–1752. doi: 10.1002/hep4.1908.
3. Riquelme, E., Zhang, Y., Zhang, L., Montiel, M., Zoltan, M., Dong, W., et al. (2019). Tumor microbiome diversity and composition influence pancreatic cancer outcomes. Cell 178, 795–806. e12. doi: 10.1016/j.cell.2019.07.008
4. Sheehan, D. H., Asam, K., Knight, N. D., Patel, J. J., Stewart, J. A., Molina, P. A., et al. (2025). Altered bacteria abundance is associated with outcomes in head and neck squamous cell carcinoma. Otolaryngol. Neck Surg. 173, 420–432. doi:10.1002/ohn.1262.
5. Nejman, D., Livyatan, I., Fuks, G., Gavert, N., Zwang, Y., Geller, L. T., et al. (2020). The human tumor microbiome is composed of tumor type-specific intracellular bacteria. Science 368, 973–980. doi: 10.1126/science.aay9189.
6. Ochi, T., Fujiki, R., Fukuyo, M., Rahmutulla, B., Nakagawa, T., Ota, M., et al. (2025). Association of intratumoral bacterial abundance with lung cancer prognosis in the Chiba University Hospital cohort. Cancer Sci. 116, 2040–2046. doi:10.1111/cas.70080.
7. Mou, W., Deng, Z., Zhu, L., Jiang, A., Lin, A., Xu, L., et al. (2025). Intratumoral mycobiome heterogeneity influences the tumor microenvironment and immunotherapy outcomes in renal cell carcinoma. Sci. Adv. 11:eadu1727. doi:10.1126/sciadv.adu1727.
8. Sepich-Poore GD, Zitvogel L, Straussman R, Hasty J, Wargo JA, Knight R. The microbiome and human cancer. Science. 2021 Mar 26;371(6536):eabc4552. doi:10.1126/science.abc4552.
9. Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillère R, et al. Gut microbiome influences efficacy of PD-1–based immunotherapy. Science. 2018;359(6371):91–97. doi:10.1126/science.aan3706.
10. Hanahan, D. (2022). Hallmarks of cancer: new dimensions. Cancer Discov. 12, 31–46. doi: 10.1158/2159-8290.CD-21-1059
11. Hanahan, D., and Weinberg, R. A. (2011). Hallmarks of cancer: the next generation. Cell 144, 646–674. doi: 10.1016/j.cell.2011.02.013.
12. Hanahan, D., and Weinberg, R. A. (2000). The hallmarks of cancer. Cell 100, 57–70. doi: 10.1016/S0092-8674(00)81683-9.
13. Tsay, J. J., Wu, B. G., Badri, M. H., Clemente, J. C., Shen, N., Meyn, P., et al. (2018). Airway microbiota is associated with upregulation of the PI3K pathway in lung cancer. Am. J. Respir. Crit. CareMed. 198, 1188–1198. doi: 10.1164/rccm.201710-2118OC.
14. Fruman, D. A., Chiu, H., Hopkins, B. D., Bagrodia, S., Cantley, L. C., and Abraham, R. T. (2017). The PI3K pathway in human disease. Cell 170, 605–635. doi: 10.1016/j.cell.2017.07.029.
15. Mann, E. R., Lam, Y. K., and Uhlig, H. H. (2024). Short-chain fatty acids: linking diet, the microbiome and immunity. Nat. Rev. Immunol. 24, 577–595. doi: 10.1038/s41577-024-01014-8.
16. Fulbright, L. E., Ellermann, M., and Arthur, J. C. (2017). The microbiome and the hallmarks of cancer. PLoS Pathog. 13:e1006480. doi: 10.1371/journal.ppat.1006480.
17. He, Y., Fu, L., Li, Y., Wang, W., Gong, M., Zhang, J., et al. (2021). Gut microbial metabolites facilitate anticancer therapy efficacy by modulating cytotoxic CD8+ T cell immunity. Cell. Metab. 33, 988–1000.e7. doi: 10.1016/j.cmet.2021.03.002.
18. Buti, L., Spooner, E., Van der Veen, A. G., Rappuoli, R., Covacci, A., and Ploegh, H. L. (2011). Helicobacter pylori cytotoxin-associated gene A (CagA) subverts the apoptosis-stimulating protein of p53 (ASPP2) tumor suppressor pathway of the host. Proc. Natl. Acad. Sci. U. S. A. 108, 9238–9243. doi: 10.1073/pnas.1106200108.
19. Lu, R., Wu, S., Zhang, Y. G., Xia, Y., Liu, X., Zheng, Y., et al. (2014). Enteric bacterial protein AvrA promotes colonic tumorigenesis and activates colonic beta-catenin signaling pathway. Oncogenesis 3:e105. doi: 10.1038/oncsis.2014.20.
20. Fridman, J. S., and Lowe, S. W. (2003). Control of apoptosis by p53. Oncogene 22, 9030–9040. doi: 10.1038/sj.onc.1207116.
21. Kastenhuber, E., and Lowe, S. (2017). Putting p53 in context. Cell 170, 1062–1078. doi: 10.1016/j.cell.2017.08.028.
22. Bieging-Rolett, K. T., Kaiser, A. M., Morgens, D. W., Boutelle, A. M., Seoane, J. A., Van Nostrand, E. L., et al. (2020). Zmat3 is a key splicing regulator in the p53 tumor suppression program. Mol. Cell. 80, 452–469.e9. doi: 10.1016/j.molcel.2020.10.022.
23. Aschtgen, M. S., Fragkoulis, K., Sanz, G., Normark, S., Selivanova, G., Henriques-Normark, B., et al. (2022). Enterobacteria impair host p53 tumor suppressor activity through mRNA destabilization. Oncogene 41, 2173–2186. doi: 10.1038/s41388-022-02238-5.
24. Roerden M, Spranger S. Cancer immune evasion, immunoediting and intratumour heterogeneity. Nat Rev Immunol. 2025;25:353–369. doi:10.1038/s41577-024-01111-8.
25. Lee, J., Roberts, J. S., Atanasova, K. R., Chowdhury, N., and Yilmaz, Ö. A. (2018). Novel kinase function of a nucleoside-diphosphate-kinase homologue in Porphyromonas gingivalis is critical in subversion of host cell apoptosis by targeting heat-shock protein 27. Cell Microbiol. 20:e12825. doi: 10.1111/cmi. 12825.
26. Jiang, S., Zhang, S., Langenfeld, J., Lo, S. C., and Rogers, M. B. (2008). Mycoplasma infection transforms normal lung cells and induces bone morphogenetic protein 2 expression by post-transcriptional mechanisms. J. Cell Biochem. 104, 580–594. doi: 10.1002/jcb.21647.
27. Alizadeh, S., Esmaeili, A., and Omidi, Y. (2020). Anti-cancer properties of Escherichia coli Nissle 1917 against HT-29 colon cancer cells through regulation of Bax/Bcl-xL and AKT/PTEN signaling pathways. Iran J. Basic Med. Sci. 23, 886–893. doi: 10.22038/ijbms.2020.43016.10115.
28. de Jesus, B. B., and Blasco, M. A. (2013). Telomerase at the intersection of cancer and aging. Trends Genet TIG. 29, 513–520. doi: 10.1016/j.tig.2013.06.007.
29. Vliet-Gregg, P. A., Robinson, K. L., Levan, J., Matsumoto, L. R., and Katzenellenbogen, R. A. (2019). NFX1-123 is highly expressed in cervical cancer and increases growth and telomerase activity in HPV 16E6 expressing cells. Cancer Lett. 449, 106–113. doi: 10.1016/j.canlet.2019.02.024.
30. Liu X, Zhang J, Yi T, Li H, Tang X, Liu D, et al. Decoding tumor angiogenesis: pathways, mechanisms, and future directions in anti-cancer strategies. Biomark Res. 2025;13:62. doi:10.1186/s40364-025-00779-x.
31. Castro, P. R., Bittencourt, L. F. F., Larochelle, S., Andrade, S. P., Mackay, C. R., Slevin, M., et al. (2021). GPR43 regulates sodium butyrate-induced angiogenesis and matrix remodeling. Am. J. Physiol. Heart Circ. Physiol. 320, H1066–H1079. doi: 10.1152/ajpheart.00515.2019.
32. Kuhn, K. A., Schulz, H. M., Regner, E. H., Severs, E. L., Hen-

drickson, J. D., Mehta, G., et al. (2018). Bacteroidales recruit IL-6-producing intraepithelial lymphocytes in the colon to promote barrier integrity. Mucosal. Immunol. 11, 357–368. doi: 10.1038/mi.2017.55.

33. Mantovani, A., Cassatella, M. A., Costantini, C., and Jaillon, S. (2011). Neutrophils in the activation and regulation of innate and adaptive immunity. Nat. Rev. Immunol. 11, 519–531. doi: 10.1038/nri3024.
34. Kostic, A. D., Chun, E., Robertson, L., Glickman, J. N., Gallini, C. A., Michaud, M., et al. (2013). Fusobacterium nucleatum potentiates intestinal tumorigenesis and modulates the tumor immune microenvironment. Cell Host Microbe. 14, 207–215. doi: 10.1016/j.chom.2013.07.007.
35. Coussens, L. M., and Pollard, J. W. (2011). Leukocytes in mammary development and cancer. Cold Spring Harb Perspect. Biol. 3:a003285. doi: 10.1101/cshperspect.a003285.
36. Li, Z. P., Liu, J. X., Lu, L. L., Wang, L. L., Xu, L., Guo, Z. H., et al. (2021). Overgrowth of Lactobacillus in gastric cancer. World J. Gastrointest. Oncol. 13, 1099–1108. doi: 10.4251/wjgo.v13.i9.1099.
37. Allgayer, H., Mahapatra, S., Mishra, B., Swain, B., Saha, S., Khanra, S.,et al. (2025). Epithelial-to-mesenchymal transition (EMT) and cancer metastasis: the status quo of methods and experimental models. Mol. Cancer 24:167. doi: 10.1186/s12943-025-02338-2.
38. Slater, E., Owen, R. J., Williams, M., and Pounder, R. E. (1999). Conservation of the cag pathogenicity island of Helicobacter pylori: associations with vacuolating cytotoxin allele and IS605 diversity. Gastroenterology 117, 1308–1315. doi: 10.1016/S0016-5085(99)70281-7.
39. Yamaoka, Y. (2010). Mechanisms of disease: Helicobacter pylori virulence factors. Nat. Rev. Gastroenterol. Hepatol. 7, 629–641. doi: 10.1038/nrgastro.2010.154.
40. Shi, Y., Yang, Z., Zhang, T., Shen, L., Li, Y., and Ding, S. (2019). SIRT1-targeted miR-543 autophagy inhibition and epithelial-mesenchymal transition promotion in Helicobacter pylori CagA-associated gastric cancer. Cell Death Dis. 10:625. doi: 10.1038/s41419-019-1859-8.
41. Sommariva, M., and Gagliano, N. (2020). E-cadherin in pancreatic ductal adenocarcinoma: a multifaceted actor during EMT. Cells 9:1040. doi: 10.3390/cells9041040.
42. Rubinstein, M. R., Wang, X., Liu, W., Hao, Y., Cai, G., and Han, Y. W. (2013). Fusobacterium nucleatum promotes colorectal carcinogenesis by modulating E-cadherin/β-catenin signaling via its FadA adhesin. Cell Host Microbe. 14, 195–206. doi: 10.1016/j.chom.2013.07.012.
43. Yu, J., Liang, Y., Zhang, Q., Ding, H., Xie, M., Zhang, J., et al. (2025). An interplay between human genetics and intratumoral microbiota in the progression of colorectal cancer. Cell Host Microbe. 33, 657–670.e6. doi: 10.1016/j.chom.2025.04.003.
44. Zhang, Q., Zhao, Q., Li, T., Lu, L., Wang, F., Zhang, H., et al. (2023). Lactobacillus plantarum-derived indole-3-lactic acid ameliorates colorectal tumorigenesis via epigenetic regulation of CD8+ T cell immunity. Cell Metab. 35, 943–960.e9. doi: 10.1016/j.cmet.2023.04.015.
45. Nakashima, C., Yamamoto, K., Kishi, S., Sasaki, T., Ohmori, H., Fujiwara- Tani, R., et al. (2020). Clostridium perfringens enterotoxin induces claudin- 4 to activate YAP in oral squamous cell carcinomas. Oncotarget 11, 309–321. doi: 10.18632/oncotarget.27424.
46. Kong, C., Yan, X., Zhu, Y., Zhu, H., Luo, Y., Liu, P., et al. (2021). Fusobacterium nucleatum promotes the development of colorectal cancer by activating a cytochrome P450/epoxyoctadecenoic acid axis via TLR4/Keap1/NRF2 signaling. Cancer Res. 81, 4485–4498. doi: 10.1158/0008-5472.CAN-21-0453.
47. Parida, S., Wu, S., Siddharth, S.,Wang, G., Muniraj, N.,Nagalingam, A., et al. (2021). A procarcinogenic colon microbe promotes breast tumorigenesis and metastatic progression and concomitantly activates notch and β-catenin axes. Cancer Discov. 11, 1138–1157. doi: 10.1158/2159-8290.CD-20-0537.
48. Fu, A., Yao, B., Dong, T., Chen, Y., Yao, J., Liu, Y., et al. (2022). Tumor-resident intracellular microbiota promotes metastatic colonization in breast cancer. Cell 185, 1356–1372.e26. doi: 10.1016/j.cell.2022.02.027.
49. Chen Y, Liu S, Tan S, Zheng Y, Chen Y, Yang C, et al. KRAS mutations promote the intratumoral colonization of enterotoxigenic Bacteroides fragilis in colorectal cancer through the regulation of the miRNA3655/SURF6/IRF7/IFNβ axis. Gut Microbes. 2024;16:2423043. doi:10.1080/19490976.2024.2423043.
50. Zheng, X., Liu, R., Zhou, C., Yu, H., Luo, W., Zhu, J., et al. (2021). ANGPTL4-mediated promotion of glycolysis facilitates the colonization of Fusobacterium nucleatum in colorectal cancer. Cancer Res. 81, 6157–6170. doi: 10.1158/0008-5472.CAN-21-2273.
51. Hong, J., Guo, F., Lu, S. Y., Shen, C., Ma, D., Zhang, X., et al. (2021). F. nucleatum targets lncRNA ENO1-IT1 to promote glycolysis and oncogenesis in colorectal cancer. Gut 70, 2123–2137. doi: 10.1136/gutjnl-2020-322780.
52. Sun, J., Tang, Q., Yu, S., Xie, M., Zheng, W., Chen, G., et al. (2023). F. nucleatum facilitates oral squamous cell carcinoma progression via GLUT1-driven lactate production. eBioMedicine 88:104444. doi: 10.1016/j.ebiom.2023.104444.
53. Berrios, C., Padi, M., Keibler, M. A., Park, D. E., Molla, V., Cheng, J., et al. (2016). Merkel cell polyomavirus small T antigen promotes pro-glycolytic metabolic perturbations required for transformation. PLoS Pathog. 12:e1006020. doi: 10.1371/journal.ppat.1006020.
54. Tzeng, A., Sangwan, N., Jia, M., Liu, C. C., Keslar, K. S., Downs-Kelly, E., et al. (2021). Human breast microbiome correlates with prognostic features and immunological signatures in breast cancer. Genome Med. 13:60. doi: 10.1186/s13073-021-00874-2.
55. Mima, K., Sukawa, Y., Nishihara, R., Qian, Z. R., Yamauchi, M., Inamura, K., et al. (2015). Fusobacterium nucleatum and T-cells in colorectal carcinoma. JAMA Oncol. 1, 653–661. doi: 10.1001/jamaoncol.2015.1377.
56. Wang, Q., Liu, Y., Chen, W., Chen, S., Su, M., Zheng, Y., et al. (2024). Uterine commensal peptostreptococcus species contribute to ido1 induction in endometrial cancer via indoleacrylic acid. Biomedicines 12:573. doi: 10.3390/biomedicines12030573.
57. Sui, H., Zhang, L., Gu, K., Chai, N., Ji, Q., Zhou, L., et al. (2020). YYFZBJS ameliorates colorectal cancer progression in Apc-Min/+ mice by remodeling gut microbiota and inhibiting regulatory T-cell generation. Cell Commun. Signal CCS 18:113. doi: 10.1186/s12964-020-00596-9.
58. Shi, Y., Zheng,W., Yang, K., Harris, K. G., Ni, K., Xue, L., et al. (2020). Intratumoral accumulation of gut microbiota facilitates CD47-based immunotherapy via STING signaling. J. Exp. Med. 217:e20192282. doi: 10.1084/jem.20192282.
59. Overacre-Delgoffe, A. E., Bumgarner, H. J., Cillo, A. R., Burr, A. H. P., Tometich, J. T., Bhattacharjee, A., et al. (2021). Microbiota-specific T follicular helper cells drive tertiary lymphoid structures

and anti-tumor immunity against colorectal cancer. Immunity 54, 2812–2824.e4. doi: 10.1016/j.immuni.2021.11.003.

60. Davar D, Dzutsev AK, McCulloch JA, et al. Fecal microbiota transplant overcomes resistance to anti-PD-1 therapy in melanoma patients. Science. 2021;371(6529):595–602. doi:10.1126/science.abf3363.
61. Martínez-Jiménez, F., Muiños, F., Sentís, I., Deu-Pons, J., Reyes-Salazar, I., Arnedo- Pac, C., et al. (2020). A compendium of mutational cancer driver genes. Nat. Rev. Cancer 20, 555–572. doi: 10.1038/s41568-020-0290-x.
62. Lim, N. R., and Chung, W. C. (2023). Helicobacter pylori-associated chronic atrophic gastritis and progression of gastric carcinogenesis. Korean J. Gastroenterol. Taehan Sohwagi Hakhoe Chi. 82, 171–179. doi: 10.4166/kjg.2023.097.
63. Cao, Y., Oh, J., Xue, M., Huh, W. J., Wang, J., Gonzalez-Hernandez, J. A., et al. (2022). Commensal microbiota from patients with inflammatory bowel disease produce genotoxic metabolites. Science 378:eabm3233. doi: 10.1126/science.abm3233.
64. Okuda, S., Shimada, Y., Tajima, Y., Yuza, K., Hirose, Y., Ichikawa, H., et al. (2021). Profiling of host genetic alterations and intra-tumor microbiomes in colorectal cancer. Comput. Struct. Biotechnol. J. 19, 3330–3338. doi: 10.1016/j.csbj.2021.05.049.
65. Giam CZ, Semmes OJ. HTLV-1 infection and adult T-cell leukemia/lymphoma: a tale of two proteins, Tax and HBZ. Viruses. 2016;8:161. doi:10.3390/v8060161.
66. Guo, P., Tian, Z., Kong, X., Yang, L., Shan, X., Dong, B., et al. (2020). FadA promotes DNA damage and progression of Fusobacterium nucleatum-induced colorectal cancer through upregulation of chk2. J. Exp. Clin. Cancer Res. CR. 39:202. doi: 10.1186/s13046-020-01677-w.
67. Pushalkar S, Hundeyin M, Daley D, et al. The pancreatic cancer microbiome promotes oncogenesis by induction of innate and adaptive immune suppression. Cancer Discov. 2018;8:403–416. doi:10.1158/2159-8290.CD-17-1134.
68. Pleguezuelos-Manzano, C., Puschhof, J., Rosendahl Huber, A., van Hoeck, A., Wood, H. M., Nomburg, J., et al. (2020). Mutational signature in colorectal cancer caused by genotoxic pks+ E. coli. Nature 580, 269–273. doi: 10.1038/s41586-020-2080-8.
69. Robles, A. I., and Harris, C. C. (2010). Clinical outcomes and correlates of TP53 mutations and cancer. Cold Spring Harb. Perspect. Biol. 2:a001016. doi: 10.1101/cshperspect.a001016.
70. Greathouse, K. L., White, J. R., Vargas, A. J., Bliskovsky, V. V., Beck, J. A., von Muhlinen, N., et al. (2018). Interaction between the microbiome and TP53 in human lung cancer. Genome Biol. 19:123. doi: 10.1186/s13059-018-1501-6.
71. Denk, D., and Greten, F. R. (2022). Inflammation: the incubator of the tumor microenvironment. Trends Cancer 8, 901–914. doi: 10.1016/j.trecan.2022.07.002.
72. DiDonato, J. A., Mercurio, F., and Karin, M. (2012). NF-κB and the link between inflammation and cancer. Immunol. Rev. 246, 379–400. doi: 10.1111/j.1600-065X.2012.01099.x.
73. Hoste, E., Arwert, E. N., Lal, R., South, A. P., Salas-Alanis, J. C., Murrell, D. F., et al.(2015). Innate sensing of microbial products promotes wound-induced skin cancer. Nat. Commun. 6:5932. doi: 10.1038/ncomms6932.
74. Goodwin, A. C., Destefano Shields, C. E., Wu, S., Huso, D. L., Wu, X., Murray- Stewart, T. R., et al. (2011). Polyamine catabolism contributes to enterotoxigenic Bacteroides fragilis-induced colon tumorigenesis. Proc. Natl. Acad. Sci. U. S. A. 108, 15354–15359. doi: 10.1073/pnas.1010203108.
75. Dejea, C. M., Fathi, P., Craig, J. M., Boleij, A., Taddese, R., Geis, A. L., et al. (2018). Patients with familial adenomatous polyposis harbor colonic biofilms containing tumorigenic bacteria. Science 359, 592–597. doi: 10.1126/science.aah3648.
76. Mou, W., Deng, Z., Zhu, L., Jiang, A., Lin, A., Xu, L., et al. (2025). Intratumoral mycobiome heterogeneity influences the tumor microenvironment and immunotherapy outcomes in renal cell carcinoma. Sci. Adv. 11:eadu1727. doi: 10.1126/sciadv.adu1727.
77. Narunsky-Haziza, L., Sepich-Poore, G. D., Livyatan, I., Asraf, O., Martino, C., Nejman, D., et al. (2022). Pan-cancer analyses reveal cancer-type-specific fungal ecologies and bacteriome interactions. Cell 185, 3789–3806.e17. doi: 10.1016/j.cell.2022.09.005.
78. Liang, Y., Li, Q., Liu, Y., Guo, Y., and Li, Q. (2023). Awareness of intratumoral bacteria and their potential application in cancer treatment. Discov. Oncol. 14:57. doi: 10.1007/s12672-023-00670-x.
79. López-Otín, C., and Kroemer, G. (2021). Hallmarks of health. Cell 184, 33–63. doi: 10.1016/j.cell.2020.11.034.
80. Park, E. M., Chelvanambi, M., Bhutiani, N., Kroemer, G., Zitvogel, L., and Wargo, J. A. (2022). Targeting the gut and tumor microbiota in cancer. Nat. Med. 28, 690–703. doi: 10.1038/s41591-022-01779-2.
81. Png, C. W., Lee,W. J. J., Chua, S. J., Zhu, F., Gastric Consortium5, Yeoh, K. G., and Zhang, Y. (2022). Mucosal microbiome associates with progression to gastric cancer. Theranostics 12, 48–58. doi: 10.7150/thno.65302.
82. Geller, L. T., Barzily-Rokni, M., Danino, T., Jonas, O. H., Shental, N., Nejman, D., et al. (2017). Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine. Science 357, 1156–1160. doi: 10.1126/science.aah5043.
83. Yu, T., Guo, F., Yu, Y., Sun, T., Ma, D., Han, J., et al. (2017). Fusobacterium nucleatum promotes chemoresistance to colorectal cancer by modulating autophagy. Cell 170, 548–563.e16. doi: 10.1016/j.cell.2017.07.008.
84. Yang, W., Chen, C. H., Jia, M., Xing, X., Gao, L., Tsai, H. T., et al. (2021). Tumorassociated microbiota in esophageal squamous cell carcinoma. Front. Cell Dev. Biol. 9:641270. doi: 10.3389/fcell.2021.641270.
85. Liu, J., and Zhang, Y. (2022). Intratumor microbiome in cancer progression: current developments, challenges and future trends. Biomark. Res. 10:37. doi: 10.1186/s40364-022-00381-5.
86. Gao, S., Li, S., Ma, Z., Liang, S., Shan, T., Zhang, M., et al. (2016). Presence of Porphyromonas gingivalis in esophagus and its association with the clinicopathological characteristics and survival in patients with esophageal cancer. Infect. Agent Cancer 11:3. doi: 10.1186/s13027-016-0049-x.
87. Liu, C. J., Chen, S. Q., Zhang, S. Y., Wang, J. L., Tang, X. D., Yang, K. X., et al. (2021). The comparison of microbial communities in thyroid tissues from thyroid carcinoma patients. J. Microbiol. Seoul Korea 59, 988–1001. doi: 10.1007/s12275-021-1271-9.
88. Xu, L., Hu, B., He, J., Fu, X., and Liu, N. (2025). Intratumor microbiomederived butyrate promotes chemo-resistance in colorectal cancer. Front. Pharmacol. 15:1510851. doi: 10.3389/fphar.2024.1510851.
89. Westman, E. L., Canova, M. J., Radhi, I. J., Koteva, K., Kireeva, I., Waglechner, N., et al. (2012). Bacterial inactivation of the anticancer drug doxorubicin. Chem. Biol. 19, 1255–1264. doi: 10.1016/j.chembiol.2012.08.011.
90. Yan, A., Culp, E., Perry, J., Lau, J. T., MacNeil, L. T., Surette, M.

G., et al. (2018). Transformation of the anticancer drug doxorubicin in the human gutmicrobiome. ACS Infect. Dis. 4, 68–76. doi: 10.1021/acsinfecdis.7b00166.

91. Miller, B. C., Sen, D. R., Al Abosy, R., Bi, K., Virkud, Y. V., LaFleur, M. W., et al. (2019). Author correction: subsets of exhausted CD8+ T cells differentially mediate tumor control and respond to checkpoint blockade. Nat. Immunol. 20:1556. doi: 10.1038/s41590-019-0528-5.
92. Yang, L., Wang, Q., He, L., and Sun, X. (2024). The critical role of tumor microbiome in cancer immunotherapy. Cancer Biol Ther. 25:2301801. doi: 10.1080/15384047.2024.2301801.
93. Sivan, A., Corrales, L., Hubert, N., Williams, J. B., Aquino-Michaels, K., Earley, Z. M., et al. (2015). Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. Science 350, 1084–1089. doi: 10.1126/science.aac4255.
94. Yang, P., Liang, G., Ni, Y., Chu, X., Zhang, X.,Wang, Z., et al. (2025). Investigating the role of intratumoral Streptococcus mitis in gastric cancer progression: insights into tumor microenvironment. J. Transl. Med. 23:126. doi: 10.1186/s12967-025-06142-w.
95. Abe, S., Masuda, A., Matsumoto, T., Inoue, J., Toyama, H., Sakai, A., et al. (2024). Impact of intratumoral microbiome on tumor immunity and prognosis in human pancreatic ductal adenocarcinoma. J. Gastroenterol. 59, 250–262. doi: 10.1007/s00535-023-02069-5.
96. Bender MJ, McPherson AC, Phelps CM, et al. Dietary tryptophan metabolite released by intratumoral Lactobacillus reuteri facilitates immune checkpoint inhibitor treatment. Cell. 2023;186:1846–1862.e26. doi:10.1016/j.cell.2023.03.018.
97. Matson V, Fessler J, Bao R, et al. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. Science. 2018;359:104–108. doi:10.1126/science.aao3290.
98. Chen, Y., Yang, L., Huang, Y., Zhu, T., Zhang, L., Cheng, M., et al. (2025). Intratumoral microbiota predicts the response to neoadjuvant chemoimmunotherapy in triple-negative breast cancer. J. Immunother. Cancer 13:e010365. doi: 10.1136/jitc-2024-010365.
99. Xie, Y., Xie, F., Zhou, X., Zhang, L., Yang, B., Huang, J., et al. (2022). Microbiota in tumors: from understanding to application. Adv. Sci. Weinh Baden-Wurtt Ger. 9:e2200470. doi: 10.1002/advs.202200470.
100. Chowdhury, S., Castro, S., Coker, C., Hinchliffe, T. E., Arpaia, N., and Danino, T. (2019). Programmable bacteria induce durable tumor regression and systemic antitumor immunity. Nat. Med. 25, 1057–1063. doi: 10.1038/s41591-019-0498-z.
101. Gurbatri, C. R., Lia, I., Vincent, R., Coker, C., Castro, S., Treuting, P.M., et al. (2020). Engineered probiotics for local tumor delivery of checkpoint blockade nanobodies. Sci. Transl. Med. 12:eaax0876. doi: 10.1126/scitranslmed.aax0876.
102. Murphy, C., Rettedal, E., Lehouritis, P., Devoy, C., and Tangney, M. (2017). Intratumoural production of TNFα by bacteria mediates cancer therapy. PLoS One 12:e0180034. doi: 10.1371/journal.pone.0180034.
103. Zheng, J. H., Nguyen, V. H., Jiang, S. N., Park, S. H., Tan, W., Hong, S. H., et al. (2017). Two-step enhanced cancer immunotherapy with engineered Salmonella typhimurium secreting heterologous flagellin. Sci Transl Med. 9, eaak9537. doi: 10.1126/scitranslmed.aak9537.
104. Young LS, Yap LF, Murray PG. Epstein–Barr virus: more than 50 years old and still providing surprises. Nat Rev Cancer. 2016;16:789–802. doi:10.1038/nrc.2016.92.
105. Ringelhan M, McKeating JA, Protzer U. Viral hepatitis and liver cancer. Philos Trans R Soc Lond B Biol Sci. 2017;372:20160274. doi:10.1098/rstb.2016.0274.
106. Gessain A, Cassar O. Epidemiological aspects and world distribution of HTLV-1 infection. Front Microbiol. 2012;3:388. doi:10.3389/fmicb.2012.00388.
107. Becker JC, Stang A, DeCaprio JA, et al. Merkel cell carcinoma. Nat Rev Dis Primers. 2017;3:17077. doi:10.1038/nrdp.2017.77.
108. Parikh HI, Koparde VN, Bradley SP, et al. The intratumoral microbiome and cancer. Cancer Res. 2024.