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Intratumoral microbiota: a new perspective in cancer initiation, development, and therapy

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Microbes have been identified as significantly impacting human health. Considerable attention has been focused on how microbiota affects cancer initiation, development, and therapeutic response. Currently, the biological functions of intratumoral microbiota have been preliminarily elucidated in tumors with high microbial abundance. However, the biological roles of the microbiota and their clinical significance in tumors with low microbial abundance, to our knowledge, remain largely unexplored. This gap in understanding is primarily due to the limited sensitivity of current detection technologies. This review provides a detailed examination of intratumoral microbiota characteristics and their interactions with the tumor microenvironment, focusing on the microbiota composition in various systems and its clinical role in different tumor types. Furthermore, the review explores the potential applications of intratumoral microbiota in cancer immunotherapy, including their role as immune enhancers, new drug delivery targets, and anticancer therapeutic agents. In conclusion, these insights may facilitate the use of microbiota for cancer diagnosis, prognosis, and the development of new therapeutic strategies.

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1. Introduction

Cancer is a significant global health issue.[1] Tumor therapy initially targets molecules like genes, DNA, and proteins and then proceeds to precise subcellular organelles, including mitochondria, endoplasmic reticulum, lysosomes, and nuclei. Mitochondria likely originated from an ancient endosymbiotic event wherein proteobacteria were engulfed to facilitate energy production and cellular metabolism,[2] which implies that bacteria can integrate into host cells and fulfill specific biological functions. The human microbiome consists of bacteria, fungi, viruses, and archaea. These organisms are abundant in the digestive tract and also present in smaller numbers in the skin, upper respiratory tract, eye, and urogenital tract, which play a key role in various tumors. To date, considerable research has focused on the

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effect of non-resident bacteria on cancer development and therapeutic response.

Recent advancements in detection methodologies, particularly next-generation sequencing for the analysis of trace DNA, have significantly improved the precision of bacterial detection within tumors and enabled the identification of specific bacterial species. These technological developments challenge the previously held assumption that the presence of bacteria was merely a consequence of contamination during detection processes. Intratumoral microbiota may either promote or inhibit cancer initiation, progression, and response to immunotherapy. The role of intratumoral microbiota in tumorigenesis depends on its composition and abundance, tumor stage, and the host's immune response. Thus, understanding the microbiota composition across various tumors and their role in cancer initiation and progression can aid in identifying new therapeutic strategies and targets, enhancing treatment efficacy.

In this review, we discuss the characteristics and composition of intratumoral microbiota, their critical role in various tumor tissues, and potential applications in cancer immunotherapy. We emphasize the progress of intratumoral microbiota across various tumors. This work identifies the microbiota as a tool for cancer diagnosis or prognosis, as well as a new therapeutic strategy.

2. Characteristics of intratumoral microbiota in tumor tissue

2.1 Diverse sources

Intratumoral microbiota can originate from three sources: (i) the primary tumor site, where the microorganisms reside in the tissue that gives rise to the tumor. For instance, *Porphyromonas gingivalis* in the oral cavity can promote oral squamous cell carcinoma progression[3] and *Helicobacter pylori* in the stomach can promote gastric cancer development;[4] (ii) normal adjacent tissues (NATs), from which the microbiota can migrate into tumor tissues. Nejman *et al.* found that the bacterial composition of tumor tissues closely resembles that of NATs;[5] (iii) circulation, through which intratumoral microbiota, primarily found in tumor and immune cells, can migrate to distant tumor tissues *via* the bloodstream. Intestinal bacteria can reach different tumor sites *via* different organ–gut axes.

2.2 High heterogeneity

Intratumoral microbiota compositions exhibit variation across different tumors. Analyses of the Cancer Genome Atlas (TCGA) database, including genome-wide and transcriptome-wide approaches, reveal characteristics of intratumoral microbiota. Nejman *et al.* demonstrated microbial composition variation in different tumors by analyzing more than 1500 patient tumor samples.[5] Galeano Niño *et al.* used 16S rDNA sequencing on 44 tumor tissues isolated from 11 patients with colorectal cancer (CRC) to reveal varying degrees of heterogeneity in CRC's intratumoral microbiota.[6] Furthermore, microorganisms were confirmed to exhibit heterogeneous spatial distribution. In addition, intratumoral microbiota composition may even vary among different subtypes of the same tumor type.[5] Intratumoral microbiota is primarily bacterial, but similar characteristics are observed in intratumoral fungi. The diversity and abundance of cancer-type-specific fungi are generally lower than those of the corresponding bacterial populations.[7] Notably, bacterial and fungal abundances, diversities, and co-occurrences are strongly positively correlated in several tumors. The tumor microenvironment (TME) may provide non-competitive spaces for microbial colonization. This contrasts with the gut, where bacterial and fungal populations compete for resources, especially under antitumor or antibiotic therapies.

2.3 Spatiotemporal dynamics of the intratumoral microbiome

The intratumoral microbiota demonstrates spatiotemporal dynamics, characterized by systematic reprogramming of its diversity, abundance, and functionality in response to tumor progression, therapeutic interventions, and alterations in the host microenvironment. Temporally, the lung cancer micro-

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biome undergoes evolution with advancing disease stages: early-stage tumors exhibit greater microbial diversity with a predominance of Actinobacteria, whereas late-stage lesions are enriched with butyrate-producing bacteria, such as Roseburia spp. Microbial-derived butyrate functions by inhibiting histone deacetylase HDAC2, enhancing H3K27 acetylation in the promoter region of the long non-coding RNA H19, and inducing M2 macrophage polarization, collectively facilitating metastatic progression.[8] Spatially, the microbiota establish heterogeneous microniches within tumors. For example, in oral squamous cell carcinoma and colorectal cancer, bacterial communities colonize hypovascularized and highly immunosuppressive microenvironments associated with malignant cells.[6] Therapeutically, interventions significantly alter the composition of the microbiome: immune checkpoint blockade (ICB) decreases microbial richness across various tumor models.[9] In contrast, shifts in the intratumoral microbiota play a critical role in modulating the efficacy of ICB. For instance, the translocation of the probiotic *Limosilactobacillus reuteri* to melanoma sites enhances the response to ICB through the production of indole-3-aldehyde (I3A), a catabolite of tryptophan.[10] In conclusion, the dynamic evolution and biological functions of intratumoral microbiota are governed by a tripartite regulation involving stage progression, therapy-induced perturbations, and metabolic feedback. Their spatiotemporal heterogeneity may offer new insights for prognostic stratification and the development of targeted interventions.

3. Progress of the intratumoral microbiota in various types of tumors

3.1 Digestive system neoplasm

3.1.1 Esophageal cancer. Esophageal cancer (ESCA) is divided into two main histological subtypes: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma.[11] Microbes such as *Fusobacteria*, *Lactobacillales*, *Clostridia*, *Proteobacteria*, and *Negativicutes* are correlated with the clinical characteristics of patients with ESCA.[12] Intratumoral microbiota enhances antitumor immunity by recruiting the infiltration of immune cells. *Streptococcus* enrichment is often linked to increased CD8+ T cell infiltration and a favorable response to anti-PD-1 therapy.[13] In addition, *Fusobacterium*, identified as a pathogen, accelerates ESCC tumorigenesis and metastasis *via* inducing DNA damage, recruiting myeloid-derived suppressor cells (MDSCs),[14] activating the NF-κβ pathway,[15] and increasing METTL3-mediated m6A methylation.[16] *Fusobacterium nucleatum* invades senescent ESCC cells, enhancing senescence-associated secretory phenotype secretion, and thereby promoting ESCC progression.[17] Li *et al.* reported that *Fusobacterium nucleatum* inhibits T cell proliferation and cytokine secretion, attenuating antitumor immunity in ESCC.[18] These findings highlight the potential for intratumoral microbes and their associated metabolites to influence the tumor immune microenvironment and the efficacy of immunotherapy.

3.1.2 Gastric cancer. The gastric cancer microbiota is characterized by reduced diversity and enriched *Oceanobacter*, *Methylobacterium*, and *Syntrophomonas* genera. *Helicobacter pylori*, a common inhabitant, is classified as a class I carcinogen by the WHO.[19] However, *Helicobacter pylori* is not the only microbe accelerating gastric cancer progression. Fu *et al.* identified *Streptococcus anginosus* as a gastric tumorigenesis-promoting pathogen (Fig. 1A).[20] Li *et al.* have demonstrated that the *Streptococcus anginosus* group consistently upregulates all metabolites associated with arginine metabolism in gastric cancer tumor specimens. This metabolic reprogramming facilitates tumor cell proliferation, migration, and invasion, while simultaneously inhibiting the differentiation and infiltration of $CD8^+$ T lymphocytes within the tumor immune


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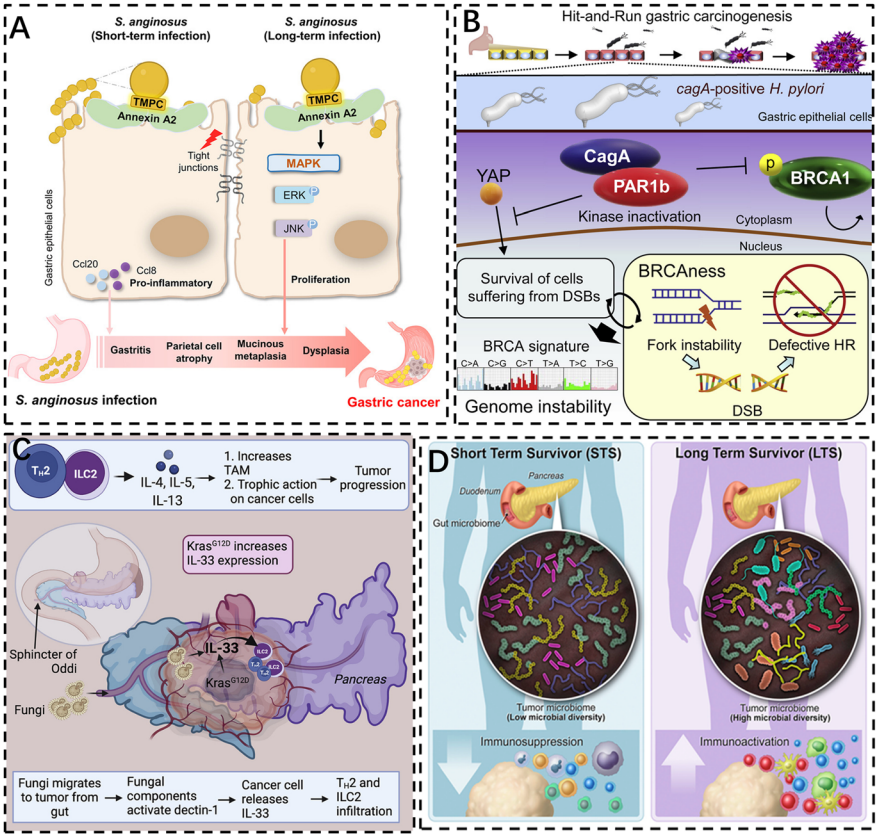

Fig. 1 (A) Schematic illustration of *Streptococcus anginosus* promoting gastric inflammation, atrophy, and tumorigenesis in mice. Reproduced with permission from ref. 20. Copyright, 2024, Elsevier Inc. (B) Schematic depiction of *Helicobacter pylori* CagA eliciting BRCAness to induce genome instability. Reproduced with permission from ref. 25. Copyright, 2021, Elsevier Inc. (C) Schematic depiction of the fungal mycobiome driving IL-33 secretion and type 2 immunity in pancreatic cancer. Reproduced with permission from ref. 52. Copyright, 2022, Elsevier Inc. (D) Schematic depiction of PDAC LTS displaying high tumor microbial diversity and immunoactivation. Reproduced with permission from ref. 54. Copyright, 2019, Elsevier Inc.

microenvironment (TIME). These processes collectively contribute to the tumorigenesis and progression of gastric cancer.[21]

Helicobacter pylori promotes gastric tumorigenesis *via* mechanisms such as DNA damage,[22] oncogenic pathway activation,[23] and induction of chronic inflammation and apoptosis.[24] Specific virulence factors, including the cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA), are critical in inducing host cell DNA damage. CagA induces DNA double-strand breaks and disrupts error-free DNA repair *via* homologous recombination, contributing to gastric carcinogenesis (Fig. 1B).[25] VacA induces vacuolization, necrosis, and apoptosis.[26] The link between gastric cancer and *Helicobacter pylori* is one of the strongest between a single bacterium and cancer causation. Prospective data indicate that *Helicobacter pylori* precedes tumorigenesis, and antibiotic eradication may reduce gastric cancer incidence.

3.1.3 Colorectal cancer. The gut microbiota, found in CRC, engages in structured crosstalk with the host, influencing multiple physiological processes. CRC-promoting bacterial species like *Fusobacterium nucleatum*, *Escherichia coli*, and *Bacteroides fragilis*, and CRC-protecting bacterial species like *Clostridium butyricum*, *Streptococcus thermophilus*, and *Lacticaseibacillus paracasei* are part of the gut microbiota and play critical roles in the development of CRC.[27]

Intratumoral microbiota produces genotoxins that damage colonic epithelial cell DNA, promoting CRC development. *Escherichia coli* harboring polyketide synthetase pathogenicity island, known to encode the genotoxin colibactin, are increasingly associated with CRC.[28–30] *Escherichia coli* that produce colibactin induce DNA breaks, cell cycle arrest, and senescence, promoting tumor growth.[31] *Campylobacter jejuni* produces a cytolethal-distending toxin that causes DNA double-strand breaks.[32] Moreover, the toxin produced by enterotoxigenic *Bacteroides fragilis* compromises colonic epithelial and barrier integrity, causing inflammation and inducing epithelial cell proliferation through activating the NF-κβ and STAT3 signaling pathways, promoting CRC progression.[33] Recent evidence suggests that the microbiota may drive tumor metastasis by regulating CRC metabolism. *Fusobacterium nucleatum*, a key periodontal pathogen, is enriched in CRC. *Fusobacterium nucleatum* subspecies animalis (Fna) exists in two distinct clades: Fna C1 and Fna C2, with only the latter shown to induce tumors and promote oxidative stress in intes-

tinal metabolism in mouse models.[34] *Fusobacterium nucleatum* activates the TLR4/Keap1/NRF2 pathway, increasing CYP2J2 and 12,13-EpOME levels, which promote tumor metastasis.[35] Cui *et al.* reported that *trans*-3-indoleacrylic acid, a tryptophan metabolite from *Peptostreptococcus anaerobius*, promotes colorectal carcinogenesis *via* inhibiting ferroptosis.[36] These studies indicate that gut microbes can indirectly affect the tumor microenvironment through metabolites or the immune system, potentially altering the composition and function of the intratumoral microbiota.

3.1.4 Liver cancer. Primary liver cancer is classified into three main histological subtypes: hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and the combined HCC-ICC.[37] HCC is the most prevalent type of liver cancer, characterized by high recurrence rates and poor prognosis.[38] Microbial diversity in HCC tissues significantly exceeds that in adjacent tissues. *Bacteroidetes*, *Firmicutes*, and *Proteobacteria* are more abundant in HCC tissues, whereas antitumor bacteria like *Pseudomonas* are less so.[39] Cai *et al.* identified *Burkholderiales*, *Pseudomonadales*, *Xanthomonadales*, *Bacillales*, and *Clostridiales* as the predominant bacterial orders in ICC. An increased presence of *Paraburkholderia fungorum* in paracancerous tissues suggests a role in ICC pathogenesis.[40]

Microorganisms contribute to HCC development *via* direct and indirect mechanisms.[41] *Stenotrophomonas maltophilia* is found in HCC patients with cirrhosis. *Stenotrophomonas maltophilia* activates the TLR4/NF-κβ/NLRP3 pathway, resulting in a senescence-associated secretory phenotype in hepatic stellate cells, which induces inflammation and promotes cirrhosis and HCC progression.[42] Sun *et al.* found that $CD68^+$ macrophages were more prevalent in areas rich in intratumoral microbiota.[43] Comparative analysis of HCC subtypes shows that the bacteria-dominant subtype increased M2 macrophage infiltration and upregulated metabolic pathways compared to the virus-dominated subtype. This infiltration of M2 macrophages correlates positively with amino acid metabolism. Notably, HCC metabolic patterns differ significantly from those in normal liver tissues, indicating that the unique microbial environments in HCC patients may influence metabolic variations.[44] These findings suggest that the intratumoral microbiota could modulate the tumor immune microenvironment through metabolic reprogramming.

3.1.5 Pancreatic cancer. The pancreatic cancer microbiome, communicating with the gut microbiome, affects the host immune response and the disease's natural history. The predominant bacterial genera in the pancreas are *Proteobacteria*, *Bacteroidetes*, and *Firmicutes*. *Enterobacteriaceae* and *Pseudomonadaceae*, identified in pancreatic ductal adenocarcinoma (PDAC), may modulate tumor sensitivity to gemcitabine (Gem).[45]

Intratumoral microbiota can remodel the tumor immune microenvironment, accelerating pancreatic cancer development. Bacteria linked to PDAC trigger innate and adaptive immune suppression, reducing the amount of MDSCs and enhancing M1 macrophage and TH1 differentiation, thereby activating $CD8^+$ T cells.[46] Indole-producing bacteria, including *Lactobacillus murinus*, elevate aryl hydrocarbon receptor transcriptional responses and promote an immunosuppressive TME in PDAC, promoting tumor growth.[47] Moreover, colonization within the microenvironment of PDAC results in the metabolic production of butyrate. This meta *Clostridium butyricum* bolite increases the susceptibility of PDAC tumor cells to ferroptosis inducers, such as RSL3. The combined therapeutic approach, utilizing either *Clostridium butyricum* colonization or exogenous butyrate supplementation alongside RSL3, synergistically amplifies the inhibitory impact on the proliferation of PDAC tumor cells.[48] *Porphyromonas gingivalis*, a key periodontal pathogen, is strongly associated with pancreatic cancer.[49] Ma *et al.* reported that *Porphyromonas gingivalis* boosts neutrophil chemokines and elastase secretion, creating a proinflammatory TME and promoting pancreatic cancer progression.[50] Saba *et al.* found that *Porphyromonas gingivalis* protects tumor cells from ROS-induced cell death due to nutrient stress, accelerating PDAC progression.[51] Intratumoral fungi stimulate IL-33 secretion and type 2 immunity, potentially promoting tumor growth (Fig. 1C).[52] *Malassezia* activates mannose-binding lectin, initiating the complement cascade and promoting PDAC progression.[53] However, the intratumoral microbiota in pancreatic cancer may not be invariably harmful, with some microbes linked to better clinical outcomes. Intratumoral microbiota may modulate immune infiltration in pancreatic cancer long-term survivors, thereby inhibiting tumor progression. Riquelme *et al.* demonstrate that gut bacteria from long-term survival patients modulate pancreatic intratumoral bacterial composition, enhance tumor $CD8^+$ T cell activation, and inhibit MDSCs and regulatory T cells (Tregs) accumulation, thereby inhibiting tumor growth (Fig. 1D).[54] Furthermore, Ghaddar *et al.* found that a subset of tumors contains somatic-cell-associated bacteria, primarily associated with tumor cells and rarely found in nonmalignant tissues.[55] This suggests that microbiome targeting may prevent oncogenesis, reverse intratumoral immune tolerance, and enhance the effectiveness of checkpoint-based immunotherapy.

3.2 Respiratory system neoplasms

3.2.1 Lung cancer. Microorganisms are closely associated with lung cancer,[56] and the predominant bacteria in lung cancer are *Proteobacteria* and *Actinobacteria*.[5] Fungi have been identified within lung cancer cells. Smokers with lung cancer have more abundant intratumoral fungi, including higher levels of *Aspergillus* and *Umbelliferae fungi*. Intratumoral fungi may serve as markers to effectively distinguish lung cancer from healthy controls, holding potential for early diagnosis. In addition, Goto *et al.* suggest that the *John Cunningham virus* may contribute to lung cancer progression.[57]

Intratumoral microbiota in lung cancer can modulate cytokine production and foster a chronic inflammatory microenvironment that promotes tumorigenesis. Tyler *et al.* reported that lung microbiota activates γδ T cells, triggering the production of IL-17 and other effector molecules that promote

inflammation and tumor cell proliferation.[58] Intratumoral microbiota can induce an immunosuppressive TME and promote lung cancer progression. Notably, reduced bacterial loads correlate with decreased Tregs, enhanced NK cell activity, and reduced lung cancer metastasis.[59] This finding highlights the importance of microbiota–immune interactions in cancer progression. Studies have revealed a Treg cell-driven mechanism underlying lung-specific immunosuppression.[60,61] Additionally, Liu *et al.* reported that the tumor-resident fungus *Aspergillus sydowi* induces IL-1β secretion and MDSC activation *via* the β-glucan-mediated Dectin-1/CARD9 pathway, thereby advancing lung cancer progression.[62] Low concentration of butyrate from the intratumoral microbiome may promote lung cancer progression and metastasis by enhancing M2 macrophage polarization and function.[63] In summary, the microbiome contributes to lung cancer through multiple biological pathways, including genotoxicity, inflammation, immune response, and angiogenesis.

3.2.2 Nasopharyngeal cancer. Nasopharyngeal carcinoma (NPC) originates from the nasopharyngeal mucosa as an epithelial carcinoma in NPC tumor tissues, where the microbiota is present, with *Corynebacterium* and *Staphylococcus* being predominant.[64,65] The NPC microbiota plays a role in intratumoral infiltration and TME remodeling. Qiao *et al.* reported a strong association between high bacterial load and reduced $CD8^+$ T cell infiltration, which contributes to an immunosuppressive environment in NPC.[66] Furthermore, patients with a high bacterial load exhibited significant proliferation dependent on cell cycling. Oral-derived microbes were significantly enriched in the nasopharynx and closely associated with epithelial EBV infection.[67] This finding suggests that blocking the translocation of microbes from the oral cavity to the nasopharynx could be a potential preventative intervention for NPC.

3.3 Reproductive system neoplasms

3.3.1 Cervical cancer. Intratumoral microbiota may promote cervical carcinogenesis by inducing immune response drivers. Human papillomavirus (HPV) is established as the primary causative agent in cervical carcinogenesis. *Chlamydia trachomatis* is recognized as a cofactor of HPV in cervical cancer. Coinfections with *Chlamydia trachomatis* are more frequently observed in patients with invasive cervical cancers.[68] Cervical cancer development involves a substantial decrease in *Lactobacillus* species and an increase in *Gardnerella vaginalis*, *Prevotella bivia*, *Porphyromonas* spp., and *Streptococcus* spp.[69] *Lactobacillus* depletion may foster a proinflammatory environment, inducing malignant cell proliferation, and increasing HPV E6 and E7 oncogene expression, promoting cervical cancer development.[70] *Lactobacillus iners*, a common species, appears to be an opportunistic pathogen.[71] Colebert *et al.* illustrate that the intratumoral colonization of *Lactobacillus iners* in cervical cancer contributes to chemoradiotherapy resistance *via* L-lactate-mediated metabolic reprogramming, which is significantly associated with decreased patient survival rates.[72] Furthermore, higher levels of *Robiginitomaculum*, *Klebsiella*, *Micromonospora*, and *Microbispora* are linked to cervical cancer mortality, while *Methylobacter* levels show an inverse relationship.[73] Microbiome relative abundance and tumor classification can predict cervical cancer prognosis.

3.3.2 Prostate cancer. Prostate cancer is the second most frequent malignancy among men worldwide.[74] Current evidence indicates that the microbiota induces an inflammatory prostate microenvironment, promoting prostate cancer development and progression.[75] Infection with *Propionibacterium* acnes activates the COX2-prostaglandin and plasminogen-matrix metalloproteinase pathways, triggering a strong inflammatory response.[76] Additionally, Ma *et al.* found *Pediococcus pentosaceus*, *Listeria monocytogenes*, and *Lactobacillus crispatus* in prostate cancer.[77] Therefore, further investigation into microbiome interaction with prostate cancer cells is warranted.

3.4 Other cancers

3.4.1 Breast cancer. Breast cancer is the most common type of cancer in women. The metabolic status of breast cancer is highly plastic, and certain microbial genera are significantly correlated with metabolic activity in cancer. Researchers found that *Porphyromonas, Lacibacter, Ezakiella, Fusobacterium*, and *Pseudomonas* are more abundant in higher-stage breast tumors compared to lower-stage tumors and healthy breast microbiota. These genera exhibit distinct features in normal and tumor tissues.[78] Additionally, Banerjee *et al.* discovered that breast cancer contains fungi, viruses, Chlamydiae, and parasites (Fig. 2A).[79]

Intratumoral microbiota may affect the tumor immune microenvironment. *Propionibacterium* is more abundant in healthy controls and NATs but is scarce in tumor tissues. Higher *Propionibacterium* levels correlate with increased T-cell activation and decreased oncogenic growth, suggesting that its absence could promote tumorigenesis by inhibiting an adaptive antitumor response and fostering a pro-tumorigenic environment. Besides directly affecting host immune responses, breast microbiota produces substances that can boost the antitumor immunity response. With a higher prevalence in non-breast cancer tissues, the *Streptococcus* genus generates cadaverine, which inhibits breast cancer invasion and epithelial–mesenchymal transition.[80] Moreover, bile acids from the microbiota in breast tumors are associated with high cell proliferation and poorer survival rates.[81] Shao *et al.* found that the microbial metabolite trimethylamine *N*-oxide activates the endoplasmic reticulum stress kinase PERK, inducing pyroptosis in malignant cells and strengthening the immune response against triple-negative breast cancer (TNBC) (Fig. 2B).[82] Furthermore, in a mouse model of spontaneous breast tumors, the presence of bacteria induces a reorganization of the actin cytoskeleton in circulating tumor cells (CTCs) in the blood. This restructuring enhances CTCs' ability to withstand fluid shear stress, promoting CTC survival and breast cancer metastasis (Fig. 2C).[78] Although present in low biomass, tumor-resident microbiota plays a crucial role in cancer metastasis, making their manipulation a potentially valuable avenue for advancing oncology care.

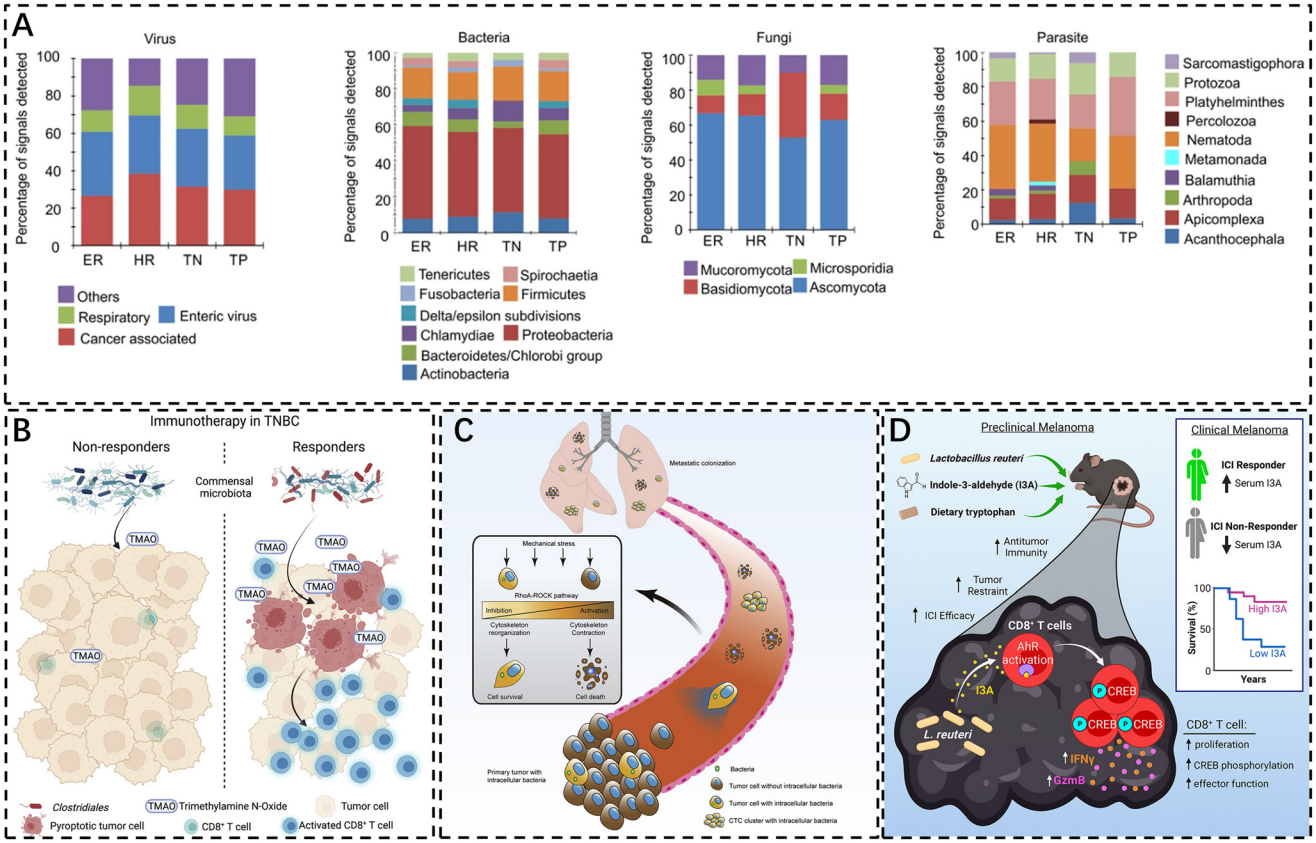

Fig. 2 (A) Bar graphs showing breast cancer containing fungi, viruses, Chlamydiae, and parasites. Reproduced with permission from ref. 79. Copyright, 2021. (B) Schematic illustration of the microbial metabolite trimethylamine *N*-oxide promoting antitumor immunity in TNBC. Reproduced with permission from ref. 82. Copyright, 2022, Elsevier Inc. (C) Schematic illustration of tumor-resident intracellular microbiota promoting metastatic colonization in breast cancer. Reproduced with permission from ref. 78. Copyright, 2022, Elsevier Inc. (D) Schematic illustration of the dietary tryptophan metabolite released by *Lactobacillus reuteri* facilitates ICI treatment. Reproduced with permission from ref. 10. Copyright, 2023, Elsevier Inc.

3.4.2 Melanoma. The cutaneous microbiota, with its potential role in melanoma development and treatment response, has emerged as a promising research area. Melanoma, a highly malignant skin tumor, has seen dramatically increased incidence rates globally.[83] Compared to other tumors, such as bone, pancreatic, and breast, melanoma has a relatively lower bacterial biomass. The predominant bacterial genera in melanoma have been identified as *Acinetobacter*, *Actinomyces*, *Corynebacterium*, *Enterobacter*, *Roseomonas*, and *Streptococcus*.[5]

Intratumoral microbiota may inhibit T cell and NK cell activation, thereby prompting melanoma development. In a mouse melanoma model, antibiotic treatment in the lung reduced bacterial load, decreased regulatory T cells, and enhanced T cells and NK cell activation, resulting in fewer lung metastases. Furthermore, recent studies implied a link between *Corynebacterium* species and melanoma progression, possibly through an IL-17-dependent pathway. Zitvogel *et al.* reported a stage-associated increase in *Corynebacterium* among 27 patients with acral melanoma by analyzing culture-based skin swabs and the patients exhibited a higher frequency of Th17 cells. These findings highlight the potential impact of the skin microbiota on local cancers.[84] Changes in microbiome composition affect immunotherapy treatment outcomes.[85] The probiotic *Lactobacillus reuteri*, which colonizes and persists within melanoma, secretes dietary tryptophan catabolite indole-3-aldehyde, stimulating an immune response. Indole-3-aldehyde activates AhR signaling in $CD8^+$ T cells, promoting interferon-γ production and enhancing the efficacy of immune checkpoint inhibitors (Fig. 2D).[10] Emerging evidence indicates that the composition and diversity of the skin microbiota critically modulate the efficacy of immune checkpoint inhibitors for skin cancer treatment.

4. Crosstalk between the intratumoral microbiota and TME

The relationship between the microbiota and tumors is highly complex, involving an intricate network of microbial infection, dysbiosis, tumorigenesis, and the TME.[86–88] The TME, encompassing tumor cells, immune cells, stromal cells, and a dense microvascular network, is the critical internal milieu essential for tumor cell existence and proliferation. Intratumoral microbiota has been identified as a crucial component of the TME.[6] The unique features of the TME including hypoxia, angio-

genesis, low pH, and immunosuppression facilitate microbial invasion and colonization. In turn, intratumoral microbiota can affect the function of tumor and immune cells and their TME, playing a critical role in cancer initiation, development, and metastasis.

4.1 Effect of the TME on microbial colonization

Several studies suggest that the microbiota migrates after cancer formation. Specific tumor microenvironments may facilitate microbial invasion and colonization. The hypoxic environment in tumors is highly favorable for the growth of facultative anaerobes and anammox bacteria, including *Clostridium perfringens*, *Escherichia coli*, *Listeria monocytogenes*, and *Bifidobacterium bifidum*.[89] Additionally, increased endothelial leakiness in tumor neovascularization facilitates microbiota entry into the tumor tissue through the bloodstream.[90] Furthermore, constantly necrotic tumor tissue provides ample nutrients for microbial reproduction. Most cancer cells depend on aerobic glycolysis, known as the Warburg effect, to provide energy for tumor growth.[91] Unlike most normal tissues, tumor cells tend to generate lactate from glucose even when oxygen is sufficient to support mitochondrial oxidative phosphorylation. The acidic environment promotes a highly immunosuppressive state in the TME. Deregulations in the tumor immune system may permit unhindered pathogen growth. These features create conducive conditions for microbiota colonization and survival.

4.2 Role of intratumoral microbiota in the TME

The International Agency for Cancer Research estimates that about 3.7×10^{30} microorganisms inhabit the earth, contributing to about 20% of human malignancies, with only 12 identified as human carcinogens.[92] Microorganisms within tumors have a dual role. On the one hand, intratumoral microbiota can promote tumor progression by inducing immunosuppression, inflammation, oncogenic signaling pathways, and host gene mutations. On the other hand, intratumoral microbiota can enhance antitumor immunity and therapeutic efficacy by activating STING, promoting tertiary lymphoid structure maturation,[93,94] and presenting microbial antigens. The role of intratumoral microbiota as a promoter or suppressor of tumors depends on its composition and abundance, tumor stage, and the host immune system response. Considering the diverse microbiota composition across tumors, targeting specific intratumoral microbiota may enable precision diagnosis, treatment, and prognosis in clinical settings.

5. Potential applications of intratumoral microbiota in cancer therapy

Given the crucial role played by intratumoral microbiota in cancer initiation and development, intratumoral microbiota can be utilized to stimulate the immune response, thus enhancing the efficacy of immunotherapy. On the other hand, intratumoral microbiota can be targeted to eliminate microorganisms at specific sites as targets, thereby enhancing precision cancer treatments.

5.1 Intratumoral microbiota as immune enhancers in immunotherapy

In recent years, immunotherapy has become a critical component in cancer treatment.[95–97] The role of intratumoral microbiota in cancer immunotherapy is increasingly recognized as studies expand. As immune enhancers, intratumoral microbiota can improve antitumor immune responses by remodeling the TME, inducing pyroptosis, and prompting tumor and immune cells to present microbial antigens, thereby enhancing the efficacy of immune checkpoint inhibitors (ICIs).[98] Intratumoral microbiota is closely linked to the host immune system response, potentially resolving current dilemmas in immunotherapy.

Eliminating certain intratumoral microbiota can convert a cold TME, thereby enhancing the immunotherapy efficacy. Qu *et al.* effectively reversed the cold TME by eliminating *Fusobacterium nucleatum*, which was then repurposed as an immune enhancer for triple-negative breast cancer (TNBC) immunotherapy. Furthermore, dead *Fusobacterium nucleatum* and non-cellular outer membrane vesicles served as immune enhancers, prompting dendritic cell maturation and T-cell infiltration, which significantly boosted the efficacy of TNBC immunotherapy (Fig. 3A).[99] Gastric cancer associated with *Helicobacter pylori* infection exhibits a higher density of PD-L1+ cells and non-exhausted $CD8^+$ T cells, suggesting that *Helicobacter pylori* promotes a hot TME and is a favorable prognostic factor for gastric cancer immunotherapy.[100] The accumulation of *Bifidobacterium bifidum* in tumors, which occurs in an interferon-dependent and STING pathway, facilitates anti-CD47 immunotherapy.[101] Zhang *et al.* analyzed 1296 intratumoral microbiome genera across samples from the TCGA database, offering a comprehensive view of the links between the intratumoral microbiome and immune features (Fig. 3B).[102] Their findings revealed that *Eudoraea* increases the abundance of active immune cells in the TME, potentially improving immune checkpoint blockade (ICB) treatment outcomes.

Intratumoral microbiota may trigger pyroptosis, thereby enhancing the efficacy of immunotherapy. Pyroptosis, a regulated form of cell death, is mediated by the pore-forming, membrane-targeting gastrin family of proteins.[103] Pyroptosis is a critical regulator in physiological processes such as inflammation, cell development, tissue homeostasis, and stress response.[104] Shen *et al.* demonstrated that intravenous administration of *Listeria monocytogenes* induces gasdermin C-dependent pyroptosis, which modifies the immunosuppressive TME and enhances the efficacy of immunotherapy by prompting a robust antitumor immune response.[105] Sun *et al.* developed an oral bacterial pyroptosis amplifier for CRC. They utilized hyaluronic acid-coated *Shewanella oneidensis* MR-1 and engineered *Escherichia coli* for tumor-specific accumu-

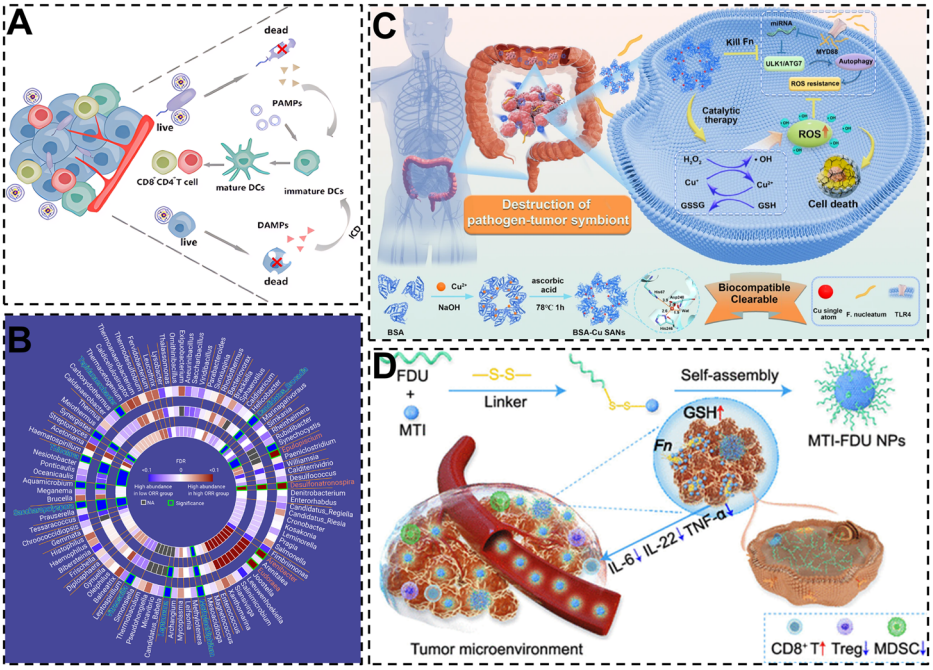

Fig. 3 (A) Schematic depiction of intratumoral bacteria reversing cold tumors for enhanced therapy of TNBC. Reproduced with permission from ref. 99. Copyright, 2023, American Chemical Society. (B) Associations between intratumoral microbiome abundance and the objective response rate at the genus, family, and order levels. Reproduced with permission from ref. 102. Copyright, 2023. (C) Schematic illustration of the synthesis of BSA-Cu SAN and its function of destroying pathogen-tumor symbionts for antitumor therapy. Reproduced with permission from ref. 126. Copyright 2023, Springer Protocols. (D) Schematic illustration of the synergistic target of the intratumoral microbiome and tumor *via* MTI-FDU. Reproduced with permission from ref. 135. Copyright 2023, American Chemical Society.

lation, leveraging hyaluronic acid's role in bacterial survival in the harsh gastrointestinal tract. This approach enhances oncolytic microbe-triggered pyroptosis, activates the gut mucosal immune response, and inhibits colon tumors and metastasis.[106]

Furthermore, the display of intratumoral bacterial peptides on host cell human leukocyte antigens (HLAs) may enable the utilization of the intratumoral microbiome in cancer immunotherapy. Microbial antigens, sharing antigenic epitopes with tumor antigens, recruit T cells specific to the microbe, which then recognize and eliminate tumor cells. Given that bacterial antigens are considered non-autologous, they may serve as targets for immunotherapy to stimulate immune responses. Kalaora *et al.* used 16S rRNA gene sequencing and HLA peptidomics to profile peptide libraries from intratumoral bacteria, revealing that tumor cells can present peptides from these bacteria to provoke an immune response.[107] Naghavian *et al.* also found that microbial peptides activate tumor-infiltrating lymphocytes (TILs) and peripheral blood memory cells, initiating an immune response.[108] TILs are essential for the success of immunotherapy and improved survival in various tumors.[109] Consequently, intratumoral microbiota can trigger an immune response *via* microbial peptides.

5.2 Intratumoral microbiota as a new target for drug delivery

Researchers are developing drug delivery systems to enhance the effectiveness of antitumor treatments.[110–113] These systems, such as liposomes, hydrogels, and nanoparticles, offer biocompatibility, prolonged circulation, and high drug-loading capacity for anticancer drugs.[114–116] Given the critical role of the intratumoral microbiota in carcinogenesis, eliminating specific pathogenic microbiota (Table 1) and restoring tumor sensitivity to ICB therapy could enhance precision cancer treatments and prevent recurrence.

5.2.1 Delivery of antimicrobial agents. Antibiotics are routinely used in clinical settings for bacterial infections. However, a single antibiotic's ability to permeate tumor cells and address bacterial infections is impeded by cell membrane barriers and the complex TME. Systemic administration of antibiotics targeting pathogenic bacteria in tumor may disrupt other microbiota in the body. Hence, precise antibiotic delivery to deplete intratumoral pathogenic microbiota without upsetting systemic microbiota imbalance is essential. Drug carrier nanoparticles can selectively target microbiota colonized within tumor cells.[120] Huang *et al.* recently developed a liposome-encapsulated silver-tinidazole complex to eliminate intratumoral bacteria using a remote loading technique. The treatment generates microbial neoantigens that enhance immune system recognition of both infected and uninfected tumor cells, triggering an antitumor immune response.[121] Yang *et al.* also developed a biomimetic nanovehicle mimicking *Fusobacterium nucleatum* for targeted antibiotic delivery.[122] This approach effectively eliminates intratumoral *Fusobacterium nucleatum* and restores tumor sensitivity to ICB therapy.

Table 1 The intratumoral microbiota serves as a target for nanodrug delivery

	Nanoplatform	Microbiota	Work	Ref.
Delivery of antimicrobial agents	LipoAgTNZ	*Fusobacterium nucleatum*, *Escherichia coli Nissle*	Eliminating intratumoral bacteria in the primary tumor and liver metastases. Generating microbial neoantigens.	121
	MTZ/Ftn-DOX@HM	*Fusobacterium nucleatum*	Eliminating intratumoral bacteria. Remodeling the TME.	122
	BSA-Cu-SAN	*Fusobacterium nucleatum*	Disrupting the pathogen–tumor symbiosis	126
	N-CSs		Reversing Gem resistance. Generating $^{\bullet}OH$ radicals.	127
	Au@BSA-CuPpIX	*Fusobacterium nucleatum*	Enhancing ROS-induced apoptosis and the therapeutic efficacy of SDT for orthotopic CRC and inhibiting lung metastasis.	128
	F. nucleatum-mimicking nanomedicine	*Fusobacterium nucleatum*	Killing intratumoral bacteria Restoring ICB therapies.	129
Co-delivery of antitumor drugs and antimicrobial agents	sNP@G/IR	*Escherichia coli* Nissle 1917	Eliminating tumor-resident intracellular bacteria Augmenting drug delivery efficacy.	134
	MTI-FDU	*Fusobacterium nucleatum*	Achieving the dual target of the intratumoral microbiota and tumor cells.	135
	PG-Pt-LA/CB(7)	*Fusobacterium nucleatum*	Eliminating *Fusobacterium nucleatum.* Enhancing chemotherapeutic efficacy.	117
	GC-DCPA-H_2O		Eliminating intratumoral microbiota. Enhancing chemotherapeutic efficacy.	118
	OLP/PP nanoassembly	*Fusobacterium nucleatum*	Eliminating *Fusobacterium nucleatum*. Inhibiting tumor growth.	119

The misuse of antibiotics has fostered the emergence of multidrug-resistant strains, complicating antibiotic-dependent treatments.[123] Recently, nanozymes have emerged as alternatives to traditional antibiotics, catalyzing reactive oxygen species (ROS) generation to kill bacteria or disrupt biofilms without inducing drug resistance.[124,125] Qin *et al.* designed protein-supported copper single-atom nanozymes (BSA-Cu-SAN) that can passively target tumors, producing ROS and depleting glutathione to promote cancer cell apoptosis. This strategy efficiently eliminates intratumoral *Fusobacterium nucleatum* and disrupts pathogen-tumor symbionts, blocking the interaction between intratumoral microbiota and tumors (Fig. 3C).[126] Gao *et al.* used nitrogen-doped carbon nanospheres (N-CSs) as nanozymes to generate hydroxyl radicals for catalytic tumor therapy. By inhibiting cytidine deaminase, the N-CSs effectively reverse Gem resistance induced by bacterial cytidine deaminase in mouse models.[127] Furthermore, Qu *et al.* designed an albumin-based nanoplatform responsive to ultrasonic stimulation. This strategy eradicated *Fusobacterium nucleatum* and promoted cancer cell apoptosis by increasing ROS levels.[128]

In addition, nanomedicines that mimic bacteria have been used to target intratumoral bacteria specifically, preserving the intestinal microbiota. Chen *et al.* created a nanomedicine mimicking *Fusobacterium nucleatum* by combining its cytoplasmic membranes with liposomes containing polymyxins. This treatment has shown promise in restoring sensitivity to ICB therapy in tumors colonized by *Fusobacterium nucleatum.*[129]

5.2.2 Co-delivery of antitumor drugs and antimicrobial agents. Some chemotherapy drugs, known to induce immunogenic cell death (ICD), can enhance the efficacy of tumor immunotherapy.[130] Observations indicate that the microbiota may contribute to resistance to chemotherapeutic drugs.[131–133] Specifically, *Gammaproteobacteria* residing in tumors can convert the chemotherapeutic drug Gem into an inactive form, reducing chemotherapy efficacy. Combining chemotherapy with immunotherapy to eliminate intratumoral microbiota may enhance the efficacy of tumor treatment. Nano-drug delivery systems hold promise for targeting lesion sites and achieving intelligent, sustained drug release. Therefore, integrating antimicrobial agents and chemotherapeutic drugs into nano-drug delivery systems could target the elimination of intratumoral microbiota and overcome drug resistance, enhancing the efficacy of antitumor therapy.

Eliminating intratumoral microbiota can increase drug delivery efficacy and, subsequently, the release of antitumor drugs, achieving a synergistic antitumor effect by dual targeting of intratumoral microbiota and tumors. Wang *et al.* designed a dual-cascade responsive nanoparticle (sNP@G/IR) containing Gem and a photothermal agent (IR1048) to enhance antitumor efficacy, with the polymer core serving an antimicrobial function. In addition, the hyperthermic effect of IR1048 aids in further eliminating tumors and bacteria.[134] Ma *et al.* designed metronidazole–fluorouridine nanoparticles (MTI-FDU) to achieve a synergistic antitumor effect. The nanoparticles metronidazole target intratumoral bacteria with minimal disruption to gut microbial homeostasis (Fig. 3D).[135] Li *et al.* developed size-tunable nanogels that integrate zinc-imidazolate frameworks with encapsulated doxorubicin (DOX) and folate grafting (f-ZIFD), combined with metronidazole. The sequential release of f-ZIFD nanoparticles from NGs promotes effective tumor penetration and precise tumor cell targeting, while the acidic-triggered intracellular release of doxorubicin enhances the antitumor effect.[136]

5.3 Intratumoral microbiota as an anticancer therapeutic agent

In the past decades, engineered strains such as *Salmonella* and *Clostridium* have effectively slowed tumor growth and metastasis,[137] enhancing survival in preclinical models and clinical cases. Bacterial-based therapies, often used as drug carriers, benefit from nanotechnology,[138] synthetic bioengineering,[139] and genetic engineering[140] to attenuate bacteria and enhance drug efficacy in oncology treatments. Recently, intratumoral bacteria have emerged as promising natural anticancer therapeutic agents. Miyako *et al.* isolated three types of intratumoral bacteria, namely *Rhodopseudomonas palustris*, *Proteus mirabilis*, and a complex bacterium of these two from CRC tissue. These isolated bacteria possess inherent biocompatibility and potent immunogenic anticancer efficacies. They selectively grow and proliferate within the tumor environment, effectively prompting immune cells to infiltrate and eliciting robust anticancer responses in mice.[141] *Staphylococcus epidermidis*, producing 6-*N*-hydroxyaminopurine, inhibits skin tumor growth.[142] Modifying these bacteria to enhance their tumor-targeting capabilities represents a promising new research direction.

6. Conclusions

Recent studies highlight the significant role of intratumoral microbiota in influencing tumor therapy outcomes. The microbiota residing within tumors can alter the tumor microenvironment, potentially impacting therapeutic efficacy. Here, we summarize the characteristics and interactions of intratumoral microbiota with various cancers, emphasizing their composition and the critical roles they play. Intratumoral microbiota consist of diverse microbial communities, which can differ markedly between tumor types and even between patients with the same cancer. For example, certain bacterial species may be more prevalent in specific tumors, influencing tumor behavior and patient response to treatment. Research has shown that these microbes can modulate immune responses, affect drug metabolism, and even alter the tumor microenvironment, potentially enhancing or inhibiting therapeutic effects.

The therapeutic applications of intratumoral microbiota are emerging as a promising area of research. Potential strategies include: (1) microbiota-based therapies: modulating the intratumoral microbiota through probiotics or targeted therapies to enhance immune responses; (2) biomarker development: identifying specific microbial signatures that correlate with treatment responses could help tailor therapies to individual patients; and (3) combination therapies: integrating microbiota modulation with existing cancer therapies, such as immunotherapy or chemotherapy, may enhance treatment efficacy. However, it is crucial to maximize the benefits of intratumoral microbiota while minimizing potential adverse effects. This requires a thorough understanding of how these microbial communities interact with cancer therapies.

Several limitations hinder the advancement of research on intratumoral microbiota. First, the low abundance of intratumoral microbiota presents challenges in obtaining adequate samples from tumor tissues. This scarcity can lead to difficulties in accurately assessing microbial diversity and composition. Secondly, current sequencing methods, such as 16S rRNA gene sequencing, primarily provide relative abundance data. This can lead to misunderstandings regarding microbial community structures and interactions. Advanced techniques like metagenomic sequencing are needed for more comprehensive insights. Additionally, enhancing the detection rate of intratumoral bacteria presents a significant challenge, as the inability to accurately identify bacterial components undermines the comprehensive assessment of microbial diversity and composition while exacerbating contamination artifacts. To address this issue, the use of microbial DNA pre-amplification through multiple displacement amplification (MDA) lowers the detection threshold to an abundance of 0.1%. Simultaneously, the application of MolYsis™ reagent kits facilitates the selective lysis of eukaryotic cells while preserving intact microbial cells. Complementary techniques, such as laser microdissection (LMD), enable precise isolation of tumor parenchymal regions, thereby reducing stromal contamination and ensuring data fidelity in studies of microbe–host interactions. Finally, establishing suitable cell and small animal models for studying intratumoral microbiota is essential for basic and preclinical research. The advancement of patient-derived organoid–bacteria co-culture systems offers a promising approach for addressing this requirement. The inherent heterogeneity of tumors and their associated microbiota complicates model development, requiring innovative approaches for replicating tumor conditions accurately.

Despite existing preclinical evidence linking intratumoral microbial modulation with immunotherapy outcomes, further research is necessary to validate these findings in clinical settings. To enhance our understanding, future investigations should focus on exploring the specific mechanisms through which intratumoral microbiota influence tumor progression, metastasis, and therapeutic responses and utilizing multi-omics technologies and refined reference databases to ensure comprehensive and accurate analyses of intratumoral microbiota. By integrating insights from microbiota research with conventional cancer therapies, we may pave the way for more effective and personalized cancer treatment strategies.

Author contributions

Huiling Liu: writing – original draft and review & editing. Zhonghui Luo: writing – original draft and review & editing. Fangzhen Luo: writing – original draft and review & editing. Xilian Wang: writing – original draft and review & editing. Hua Wei: writing – original draft and review & editing. Cui-Yun Yu: writing – original draft and review & editing.

Conflicts of interest

All authors confirmed that they have no conflicts of interest.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review (**PM-REV-02-2025-000045.R1**).

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