Received: 7 April 2024 | Accepted: 25 September 2024

DOI: 10.1002/agm2.12359

Aging Medicine Open Access WILEY

REVIEW ARTICLE

Intratumoral microbiota as cancer therapeutic target

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Funding information
National Natural Science Foundation of China, Grant/Award Number: 52273281 and 82203534; National High Level Hospital Clinical Research Funding, Grant/Award Number: BJ-2022-196

Abstract

Intratumoral microbiota, which affects the physiological and pathological processes of the host, has attracted increasing attention from researchers. Microbials have been found in normal as well as tumor tissues that were originally thought to be sterile. Intratumoral microbiota is considered to play a significant role in the development of tumors and the reduction of clinical benefits. In addition, intratumoral microbiota are heterogeneous, which have different distribution in various types of tumors, and can influence tumor development through different mechanisms, including genome mutations, inflammatory responses, activated cancer pathways, and immunosuppressive microenvironments. Therefore, eliminating the intratumoral microbiota is considered one of the most promising ways to slow down the tumor progression and improve therapeutic outcomes. In this review, we systematically categorized the intratumoral microbiota and elucidated its role in the pathogenesis and therapeutic response of cancer. We have also described the novel strategies to mitigate the impact of tumor progression. We hope this review will provide new insights for the anti-tumor treatment, particularly for the elderly population, where such insights could significantly enhance treatment outcomes.

KEYWORDS
cancer therapeutic target, elderly population, intratumoral microbiota

1 | INTRODUCTION

Infection is one of the major causes of illness especially in aging population who has weakened immunity and declined clearance capacity of pathogen. The elderly are more vulnerable to microbial infections and are at a higher risk of suffering infectious diseases than the younger. The expanding knowledge of the human microbiota has unveiled that a multitude of microorganisms inhabit various human tissues, although it was widely accepted that tissues were germ-free, including tumor tissues. More studies have shown that microbials occupy a critical role in shaping the tumor microenvironment, which have been shown to exert a profound impact on the

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development and progression of cancer.[1–3] Moreover, empirical studies have consistently indicated that modulating the microbial population lead to a significant reduction in the prevalence of tumorigenesis. A compelling example is the eradication of Helicobacter pylori, which has been linked to a substantial decrease in the risk of gastric cancer,[4,5] immunization with vaccines targeting human papillomavirus (HPV) has been correlated with a reduced frequency of cervical cancer among females.[6] Therefore, microbiota is emerging as a critical factor influencing the development of tumors. Exploring the mechanisms of intratumoral microbiotas in the process of tumors occurrence and development can deepen our comprehension of tumor oncogenesis and the factors affecting cancer therapeutics. Such advancements have the potential to refine cancer treatment modalities that especially benefits aging population.

2 | HUMAN MICROBIOTA AND DISEASE

The human microbiota is a sophisticated ecosystem that is predominantly consists of bacterial, fungi, and viruses. These microbiotas are omnipresent, occupying various parts of the body including the intestinal tract, skin, and mucosal surfaces. They coexist in a symbiotic relationship with the host organism, exerting a profound influence on both physiological and pathological processes.[7] The gut microbiota, under normal conditions, plays a vital role in providing essential nutrients, participating in metabolic processes, preserving the integrity of the mucosal barrier, and enhancing the functionality of the immune system. An imbalance in the gut microbiota, however, can precipitate and exacerbate a range of diseases in humans. Alzheimer's disease, which predominantly affects the elderly population, is associated with the dysregulation of intestinal microbiota. This disruption of the gut microbiota can compromise the barrier function of the intestinal wall, leading to increased permeability and the translocation of inflammatory substances, which can initiate and sustain a systemic, chronic inflammatory state, which is believed to contribute to the advancement of Alzheimer's disease.[8] In addition, the microbiota residing on the mucous membrane and skin surface can also cause skin inflammation and infection. Therefore, the microbiota is closely related to the physiological and pathological mechanisms of human beings.

The microbiota in the tumor was first discovered in the 19th century, but due to the limitations of the level of microbiological research, little progress has been made until the in-depth understanding of the tumor microenvironment in recent years with the assistance of sequence technologies.[9] It has been recently realized that the intratumoral microbiota is a critical determinant factor affecting the occurrence and development of the tumor. For example, Porphyromonas gingivalis (Pg) in the oral cavity can promote the initiation and progression of pancreatic cancer by modulating the immune microenvironment with pancreatic cancer.[10] Enterotoxigenic Bacteroides fragilis (ETBF) can induce inflammation and promote tumor formation by release pro-inflammatory fragile bacilli toxin, a pro-inflammatory agent that engages in multiple signal transduction pathways within colonic epithelial cells, including the activation of the mitogen-activated protein kinase (MAPK) pathway.[11–13] Nejman et al. also identified a diverse array of bacterial species across over 1500 samples from seven different types of cancer, encompassing breast, lung, ovarian, pancreatic, melanoma, bone, and brain cancers, which showed that intratumoral microbiota is widespread.[14] Therefore, in this review, we summarize the different types of microbiota in the tumor and their effects on tumor progression. We also sort out the current methods of eliminating the microbiota in the tumor aimed to offer novel strategies and insights that could inform subsequent cancer diagnostic and therapeutic practice.

3 | CHARACTERISTIC OF INTRATUMORAL MICROBIOTA

With the application of second-generation gene sequencing technology, various genera of intratumoral microbiota have been accurately subdivided and quantified.[15] Nejman et al. found that the types of microbiota in different types of cancers were different through a comprehensive analysis of the intratumoral microbiota of seven different cancer types, including breast, lung, ovary, pancreatic, melanoma, bone, and brain cancers. Additionally, it has been observed that intratumoral microbiota mainly exist within immune cells and tumor cells, exerting an influence on tumorigenesis and tumor progression via modulation of autophagy in tumor cells and the functionality of immune cells.[14]

3.1 | Bacteria

Tumors exist a variety of microbiota, with bacteria being the most abundant and typically localized within immune and tumor cells. These microbiota display tumor-specific properties, and their composition and characteristics differ across various types of cancers.

Pancreatic cancer, characterized by a fibroinflammatory microenvironment due to its inflammation-driven nature,[16] has been the subject of research regarding the presence of bacteria. Nilsson et al. conducted that Helicobacter pylori DNA was detected in the pancreas of 75% of pancreatic cancer patients.[17] However, subsequent studies did not identify specific alterations in bacterial colonies within pancreatic cancer.[18,19] It was not until 2018 that Pushallkar utilized 16S rRNA sequencing technology to analyze the microbiota of human pancreatic cancer and adjacent normal tissues, revealing a high abundance of Pseudomonas and Elizabethkingia in all pancreatic ductal adenocarcinoma (PDAC) specimens.[20] Subsequent research has further validated the presence of distinctively enriched bacteria in pancreatic cancer.[21–23]

Colorectal cancer is a type of intestinal malignancy, with its pathogenesis closely linked to disruptions in the intestinal microbiota. Fusobacterium nucleatum (Fn) has been extensively researched in the context of colorectal cancer, as it plays a significant role in the initiation, progression, and metastasis of the disease, as well as

impacting the resistance of colorectal cancer to chemotherapy.[24] Except to Fusobacterium nucleatum, recent studies have identified other microbiota associated with colorectal cancer, such as Providencia and Bifidobacteria.[25] These findings have expanded our understanding of the microbial diversity present in colorectal cancer. Furthermore, investigations into the colorectal cancer microbiota have revealed variations not only within different types of cancers but also between distal and proximal cancers. For instance, Prevotella and Firmicutes are more prevalent in proximal cancer, while Bacteroidetes are predominantly found in distal cancer.[26] These distinctions may account for the discrepancies observed in research outcomes across different studies.

Breast cancer is characterized by a diverse array of bacterial species present in tumor tissues.[14] For example, Xuan et al. identified Methylobacterium radiotolerans was abundant in tumor tissues, while Sphingomonas yanoikuyae was prevalent in paired normal tissues.[27] Fu et al. demonstrated an enrichment of Staphylococcus, Lactobacillus, Enterococcus, and Streptococcus in tumor tissues.[28] Furthermore, Smith et al. investigated the microbial of breast tissue in non-Hispanic black and non-Hispanic white patients, revealing variations in microbial based on race, stage of cancer, and breast tumor subtype.[29]

Moreover, Firmicutes, Bacteroidetes, Fusobacteria, and Actinobacteria have been found to be enriched in gastric cancer,[30] while Lachnoclostridium and Gelidibacter are associated with melanoma,[31] Streptophyta are prevalent in renal cell carcinoma.[32] Additionally, Fusobacteria have been identified in esophageal squamous cell carcinoma.[30] These findings indicate variations in bacterial species and their abundance within tumors compared to normal tissues, as well as among different types of tumors. Consequently, investigating the microbial differences across various tumor types may enhance future tumor detection methods.

3.2 | Fungus

As a symbiotic microbiota within the humans, fungi engage in resource competition with bacteria in healthy tissues to maintain a balanced microbiota. However, within the tumor microenvironment, various fungi species tend to coexist with specific bacterial strains, indicating a potential conducive environment for the growth of both fungi and bacteria. Consequently, there is a growing interest in the role of fungi within tumors. Haziza et al. conducted a comprehensive classification and analysis of fungi across more than 17,000 tissue and blood samples from 35 different cancer types, revealing the presence of fungi in all cancer types, with specific fungal types correlating with particular cancers.[33] For instance, Aspergillus and Malassezia are prevalent in breast cancer. Similarly, Anders et al. research on gastrointestinal tumors, lung cancer, and breast cancer identified the presence of Candida, Blastomyces, and Malassezia fungi.[34] In addition, Aykut et al. found the enrichment of Malassezia in both mouse and human pancreatic ductal adenocarcinoma (PDAC).[35] The fungal polysaccharides produced by Malassezia can bind to mannose-binding lectin and activate the complement cascade reaction to promote the progress of PDAC. Liu et al. found that A. sydowii can promote lung tumor progression by promoting myeloid derived suppressor cells (MDSCs) and regulating the production and recruitment of regular T cells (Treg).[36]

4 | MECHANISMS OF INTRATUMORAL MICROBIOTA IN TUMOR DEVELOPMENT AND TREATMENT

Intratumoral microbiota have been proved to be widespread in tumors, which have the ability to infiltrate various tissues via diverse routes, including migration from mucous membrane, normal adjacent tissue (NATS) and hematogenous spread.[37] An increasing number of evidences show that intratumoral microbiota can affect the initiation, progression and metastatic of tumor through a variety of mechanisms.[38] Moreover, they are capable of contributing to drug resistance in tumors by metabolizing chemotherapeutic agents or modulating the tumor microenvironment, which may ultimately result in diminished clinical outcomes from cancer treatments.

4.1 | Effect of intratumoral microbiota on tumor occurrence and development

The impact of intratumoral microbiota on tumorigenesis and its underlying mechanisms have been partially elucidated. Current results among researchers suggest that intratumoral microbiota primarily influences tumor occurrence and progression through three main avenues.[39] First, microbiotas can directly induce mutations by causing DNA damage in tumor cells, thereby elevating the risk of cancer development.[40–42] For instance, certain members of Enterobacteriaceae produce colibactin, a compound known to induce DNA damage and promote tumorigenesis.[43] Additionally, Enterotoxigenic Bacteroides fragilis (ETBF), which can also cause DNA damage through toxin production. Dejea et al. have shown that patients with familial adenomatous polyposis exhibit a high presence of ETBF and Escherichia coli in their colonic mucosa, leading to increased DNA damage in mice harboring these bacteria.[11] Second, microbiota can impact tumor progression by activating carcinogenic pathways. For instance, some tumor-associated microbiota influence the secretion of cytokines like interleukin-6 (IL-6) and tumor necrosis factor-γ (TNF-γ), triggering a pro-inflammatory response that activates pathways such as nuclear factor kappa-B (NF-κB) or signal transducer and activator of transcription 3 (STAT3) to facilitate tumor progression. Additionally, intratumoral microbiota can directly stimulate tumor development by activating cellular pathways which promote cancer growth. For example, Kong et al. identified a pathway in sclerotinia sclerotiorum that induces colorectal cancer by activating the TLR4/Keap1/

NRF2 signaling pathway to increase levels of cytochrome P450 2J2 (CYP2J2)/12,13-epoxyoctadecenoic acid (12,13-EpOME) axis, which finally promotes the development of colorectal cancer.[44] Lastly, intratumoral microbiota can enhance tumor progression and immune evasion by modulating the tumor immune microenvironment. They can influence immune checkpoints, create an immunosuppressive niche, and impact the function of immune cells within the tumor. For instance, Gur et al. have demonstrated that fatty acid binding protein 2 (FABP2) expressed by Clostridium nuclei binds to the checkpoint protein T cell immunoglobulin and ITIM domain (TIGIT), inhibiting the anti-tumor activity of natural killer (NK) cells and T cells.[45] Moreover, intratumoral microbiota can alter the recruitment of immunosuppressive cells, with evidence suggesting that certain bacteria promote the influx of myeloid-derived suppressor cells (MDSC).[20,46–48] Conversely, the removal of bacteria has been shown to enhance the differentiation of M1-like macrophages and T helper (Th) cells, indicating that the elimination of bacterial may partially alleviate the immunosuppressive niche of the tumor microenvironment.

4.2 | Effect of intratumoral microbiota on tumor metastasis

Tumor metastasis is a multifaceted and intricate process that involves various stages. To navigate the challenges posed by physical, chemical, and biological barriers during metastasis, cancer cells often adapt their inherent mechanisms to thrive in adverse conditions. This adaptation primarily involves the epithelial–mesenchymal transition (EMT), upregulation of adhesion-related genes, and reinforcement of stress resistance, all of which can be modulated by intratumoral microbiota.[37,49–51] For instance, in human breast cancer cell lines, toxins released by fragilis bacteria within tumors can induce the upregulation of EMT-related genes, such as Slug and Twist, leading to the transformation of tumor cells into migratory and invasive phenotypes.[52] Similarly, in human colorectal cancer cell lines, Clostridium species significantly enhance the adhesion between cancer cells and endothelial cells by increasing the expression of the adhesion molecule Intercellular cell adhesion molecule-1 (ICAM1).[53] This heightened adhesion facilitates cancer cell extravasation and the initiation of new metastases during experimental tail vein injections. Recent research in mouse tumor models has revealed that intratumoral microbiota trigger a response to fluid shear stress upon invading host cancer cells, a phenomenon linked to the bacteria's ability to promote metastasis. Cancer cells harboring bacteria can disseminate these microbiota to distant organs, thereby supporting cancer cell survival.[28] Apart from influencing tumor functionality, intratumoral microbiota can also impact the formation of the pre-metastatic niche (PMN). Studies focusing on colorectal cancer have demonstrated that bacteria residing within tumors can modulate the intestinal vascular barrier through the virulence factor (VirF).[54] The compromised vascular barrier, characterized by increased PV-1 expression, facilitates bacterial spread from primary colorectal tumors to the liver, establishing a PMN before the arrival of cancer cells. Elevated PV-1 levels in patients are associated with higher bacterial colonization and increased distant metastasis. Furthermore, in addition to shaping the PMN, certain soluble molecules produced by bacteria can influence its composition. Exosomes containing miR-1246/92b-3p/27A-3p and CXC motif chemokine ligand 16 (CXCL16), isolated from human colon cancer cells invaded by pseudomonas, regulate colon cancer cell migration and significantly enhance lung metastasis by targeting glycogen synthase kinase 3-β (GSK3-β) and activating the WNT-β-Catenin signaling pathway.[55]

4.3 | Effect of intratumoral microbiota on cancer therapies

At present, the main methods of tumor treatment are chemotherapy, radiotherapy, and immunotherapy. Intratumoral microbiota not only directly affects the occurrence and development of tumor, but also affects the therapeutic effect of tumor. It can induce chemotherapy resistance of tumor by directly affecting the metabolism of tumor cells.[56] For example, in patients with colorectal cancer, *F.* nucleatum, the most important intratumoral microbiota, has also been shown to promote the development of oxaliplatin resistance during treatment, by inducing autophagy.[57] At the same time, intratumoral bacteria can also induce tumor chemotherapy resistance by inducing tumor immunosuppressive microenvironment. Ma et al. evaluated the microbiota composition of breast tumors and found that enterotoxigenic Bacteroides fragilis (ETBF) was highly enriched in the tumors of patients who did not respond to taxane-based neoadjuvant chemotherapy. ETBF, albeit at low biomass, secreted the toxic protein Bacteroides fragilis toxin-1 (BFT-1) to promote breast cancer cell stemness and chemoresistance.[58] Moreover, there are few studies on the effect of intratumoral microbiota on chemotherapy, but there is also evidence that intratumoral microbiota also hinders the response to radiotherapy, such as oral administration of vancomycinsensitive bacteria, Lachnospiraceae, leads to elevated butyric acid levels in the whole body and tumor sites, thus reducing the efficacy of ionizing radiation.[59] As another major treatment of tumor at present, immunotherapy plays a vital role in tumor treatment. As an important part of tumor microenvironment, intratumoral microbiota can directly affect tumor progression by affecting tumor immunity and greatly affect the effect of immunotherapy. For example. The combination of oral Megasphaera sp.XA511 and anti-PD1 treatment was found to significantly inhibit tumor growth in the 4 T1 tumor-bearing mouse model.[60] Therefore, intratumoral microbiota is an important factor affecting tumor occurrence, development, and treatment prognosis. Exploring the mechanism of intratumoral microbiota on tumor occurrence and development provides new clues and possibilities for subsequent intratumoral microbiota intervention and tumor prognosis.

5 | ELIMINATION OF INTRATUMORAL MICROBIOTA

Intratumoral microbiota has been demonstrated to influence tumor initiation and progression, as well as impact the responsiveness of tumors to chemotherapy and immunotherapy. Concurrently, clinical observations have indicated that eradicating microbiota within tumors can prevent and manage microbiota-induced cancers like gastric, liver, and cervical cancers.[61–63] The specific elimination of intratumoral microbiota could enhance the efficacy of treatments for colorectal cancer that are susceptible to bacterial induced drug resistance.

5.1 | Antibiotic

Currently, the eradication of pathogenic bacteria in humans primarily relies on the administration of various antibiotics. Research has indicated that antibiotics can impede tumor growth. Metronidazole (MTI), a 5-nitroimidazole antibiotic, is commonly utilized for combating a range of anaerobic bacteria. Given that the interior of tumors lacks oxygen, anaerobic bacteria predominantly inhabit tumors, making MTI a potential therapeutic agent for regulating the intratumoral microbiota. Bullman et al. observed that application of MTI in the patient-derived xenografts (PDX) model enriched with Clostridium leading to notably diminish of Clostridium in tumors.[64]

Although antibiotics exhibit a beneficial impact on controlling tumor progression, their overuse may disrupt the balance of extratumoral microbiota, leading to adverse effects such as diarrhea, dyspepsia, gastrointestinal disorders, and inflammation.[65] Additionally, imbalances in extratumoral microbiota that occur with aging can lead to a variety of health issues, including weakened immune function, Alzheimer's disease, and enteritis.[8] Antibiotics can alter the equilibrium of extratumoral microbiota, which can potentially influencing secondary bile acid metabolism and consequently impacting tumor metastasis.[66] Hence, the targeted elimination of intratumoral bacteria by antibiotics poses a critical clinical challenge. Consequently, Gao et al. devised metronidazole fluorouracil nanoparticles (MTI-FDU) that enable the selective accumulation and release of drugs at the tumor site based on the enhanced permeability and retention effect (EPR) of solid tumor tissue. Leveraging the tumor's hypoxic, acidic, and high glutathione (GSH) levels, the authors incorporated a GSH-responsive linkage to achieve targeted tumor therapy.[67] In addition to nanoparticle packaging of antibiotic drugs, antibiotics can also be encapsulated within liposomes. For instance, Wang et al. engineered an antibiotic-silver complex enclosed in liposomes (LipoAgTNZ), which effectively eliminates intratumoral microbiota in primary tumors and liver metastases without disrupting intestinal microbiota.[68] Chen et al. have devised a biomimetic carrier with Fusobacterium nucleatum cytoplasmic membrance to efficiently transport antibiotics to breast cancer tumors containing Fusobacterium nucleatum, thereby mitigating the impact of antibiotics on normal flora in vivo.[69]

5.2 | Bacteriophage

Antibiotics possess a wide range of activity and can eliminate bacteria without discrimination. While efforts have been made to enhance their specificity through techniques such as nanocrystallization or liposome encapsulation, there remains a quest for more precise targeting methods. Consequently, bacteriophages have emerged as a promising tool for selectively targeting particular bacterial.[27] Xue et al. have engineered bacteriophages capable of specifically recognizing Clostridium nucleatum and silver nanoparticles for bactericidal activity, thereby developing bacteriophages that can precisely target tumor sites colonized by Clostridium nucleatum.[70] Additionally, bacteriophages, being bacterial viruses, can elicit an effective immune response and anti-tumor immunity. Zheng et al. encapsulated irinotecan, a frontline drug against colorectal cancer (CRC), within dextran nanoparticles (DNPs) to create IRT-loaded DNPs (IDNPs). Through a bioorthogonal reaction, they covalently linked azodibenzocyclooctyne (DBCO)-modified IDNPs (D-IDNPs) to azide-modified phages (A-phages) to fabricate a phage-guided biotic-abiotic hybrid nanosystem. Bacteriophages can selectively target Clostridium nucleatum, accumulate in tumor tissue in vivo, effectively suppress the growth of Clostridium nucleatum, and significantly enhance the efficacy of CRC chemotherapy.[71] However, the safety concerns associated with bacteriophages have not been entirely resolved. While bacteriophages can be sterilized, their primary mode of action involves disrupting the bacterial cell wall, which may lead to the release of lipopolysaccharide from Gram-negative bacteria, causing symptoms such as fever, systemic inflammation, and potentially shock upon entering the bloodstream.[72] Furthermore, research by Sweere et al. has demonstrated that filamentous Pseudomonas phages can directly interact with human leukocytes, resulting in phage RNA production and the stimulation of interferon production. Consequently, bacteriophages still face challenges in effectively targeting intratumoral microbiota (Figure 1).[73]

6 | CONCLUSION

As a critical constituent of the tumor microenvironment, intratumoral microbiota has received extensive attention. Numerous researchers contributed to the impact of intratumoral microbiota on the tumor emergency and development. Studies have revealed that intratumoral microbiota is heterogeneous, which exhibit different distributions across different tumor types and affecting the occurrence and development of tumors through different mechanisms. Findings suggest that intratumoral microbiota promote tumor growth mainly by directly inducing genomic mutation, triggering inflammation, activating cancer-promoting pathway, and

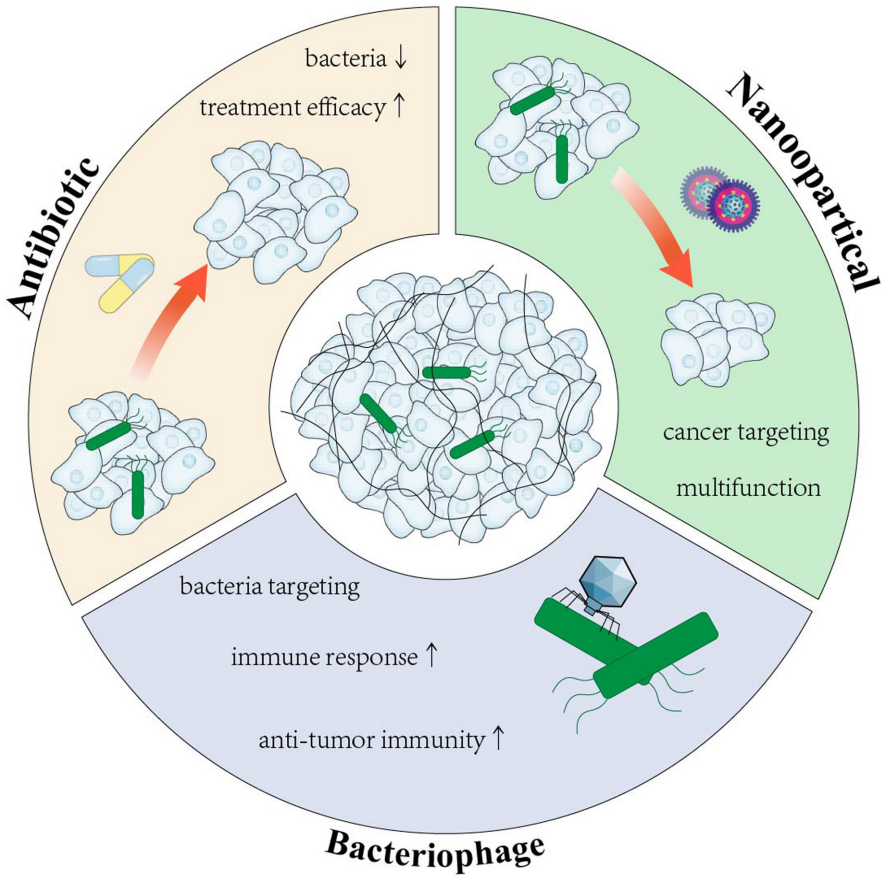

FIGURE 1 Three strategies to eliminate intratumoral microbial. Antibiotics can eliminate the intratumoral bacteria and enhancing the effectiveness of tumor treatment; Antibiotic-derived nanoparticles enhance the cancer targeting of drugs and can be designed to combine multiple functions, offering greater clinical benefits. Bacteriophage target particular types of intratumoral microbes, which reduce the impact of antibiotics on normal microbial while improving the immune response and increasing anti-tumor efficacy.

creating an immunosuppressive microenvironment. Furthermore, intratumoral microbiota can also promote tumor metastasis and colonization by enhancing the tumor's adaptability to adverse conditions and regulating pre-metastatic niche. Consequently, the elimination of intratumoral microbiota emerges as a promising strategy to impede tumor progression.

Furthermore, as one of the most important risk factors of cancer, there are enough evidences to show that the risk of cancer increases with age.[74,75] Concurrently, older individuals often face a more severe outlook when battling tumors compared to their younger counterparts, yet the underlying reasons for this disparity remain elusive. The concept of intratumoral microbiota has emerged as a novel factor that could shed light on this issue. Researches show that the increase of age will lead to the imbalance of microbiota in the elderly,[76] and the increase of age will lead to the weakening of the immune system,[77] which may affect the stability of the intratumoral microbiota and their interaction with the host immune system. Additionally, age-related chronic inflammation may change the tumor microenvironment,[78] thus affecting the composition of intratumoral microbiota. In addition, with the increase in age, the metabolic pathway of humans will change,[79] which may affect the metabolic activity of intratumoral microbiota and their effects on tumor cells. Therefore, understanding the link between age and intratumoral microbiota is a pressing matter that could alter our comprehension of cancer in the elderly and enhance the efficacy of treatments for age-related tumors.

Although there is complex crosstalk between intratumoral microbiota and tumor, there has been evidence that it is effective to treat tumor by modifying or manipulating intratumoral microbiota, and eliminating intratumoral microbiota may improve the therapeutic effect of tumor. Moreover, the way to eliminate the intratumoral microbiota could beyond antibiotics or bacteriophages. However, there are still many problems to be solved, as a broad-spectrum antimicrobial agent, antibiotics will affect the whole-body microbiota balance, especially the intestinal microbiota.[80] Intestinal microbiota disorders can lead to a series of health problems.[81] Therefore, the utilization of nanosized antibiotics is a very intelligent way to manage intratumoral bacteria. We believe that looking for drugs or methods with better targeting or narrower antibacterial spectrum are future research directions for the treatment of intratumoral microbiota.

Now, the study of intratumoral microbiota is still in a preliminary stage, and more complex and pathological animal models are needed to be used for preclinical research in the future, in order to provide a theoretical basis for clinical practice. Meanwhile, as a specific index of tumor type, intratumoral microbiota may be used as a tumor marker or a new target for early cancer screening in the future. To establish effective methods of tumor prevention and screening, we should further explore the relationship between tumor clinical diagnosis and intratumoral microbiota. It is also necessary to further explore the effect of intratumoral microbiota on different tumor therapies, which might provide new discoveries to improve the efficacy of current therapies.

AUTHOR CONTRIBUTIONS

Dr. Jie Ma devised the review, the main conceptual ideas, and proof outline, and critically reviewed the article for intellectual content. Qi An, Dr. Lu-yao Zhang, Dr. Xun-dong Wei, Dr. Jing Xu, Dr. Jiang-yong Yu, Dr. Guo-ju Wu, contributed to the writing and revisions. Chang Guo collected the information and wrote the manuscript.

ACKNOWLEDGMENTS

We would like to thank for financial support from National Natural Science Foundation of China and National High Level Hospital Clinical Research Funding.

FUNDING INFORMATION

This work was supported by National Natural Science Foundation of China [Grant No.52273281, No.82203534]; National High Level Hospital Clinical Research Funding [Grant No.BJ-2022-196].

CONFLICT OF INTEREST STATEMENT

The author declares no relevant financial or non-financial interests to disclose.

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How to cite this article: Guo C, An Q, Zhang L-y, et al. Intratumoral microbiota as cancer therapeutic target. *Aging Med*. 2024;7:636-644. doi:10.1002/agm2.12359