Acta Pharmaceutica Sinica B 2026;16(5):2877−2902

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com

REVIEW

Analysis of intratumoural bacteria: Opportunities and challenges for cancer therapy

Xiaowen Jiang[a,b], Chunyan Zhang[c], Simeng Cao[a], Yeheng Peng[a], Mingyi Zhao[b], Xuyao Zhang[a,d,*], Yuan Gao[a,d,*]

[a]*School of Pharmaceutical Science, Fudan University, Shanghai 201203, China*
[b]*School of Clinical Pharmacy, Shenyang Pharmaceutical University, Shenyang 110016, China*
[c]*Department of Stomatology, Qingdao Municipal Hospital, Qingdao 266011, China*
[d]*State Key Laboratory of Advanced Drug Formulations for Overcoming Delivery Barriers, Shanghai 201206, China*

Received 7 July 2025; received in revised form 4 September 2025; accepted 30 September 2025

KEY WORDS

Intratumoural bacteria;
Prognostic biomarkers;
Engineered bacteria;
Microbial sequencing;
Drug vector;
Immunotherapy;
Relative abundance;
Antibiotics

Abstract Intratumoural bacteria have been shown to play conflicting roles within tumours, especially in the modulation of immune responses. Moreover, bacteria have been linked to a variety of cancer types and have different prognostic values depending on the cancer. This heterogeneity is not only shaped by tumour molecular subtypes, spatial location, cancer progression stage, genetic alterations, and the presence of multiple subclones, but is also influenced by variations in angiogenesis, oxygen levels, microbial sources, endocytosis and micropinocytosis. In this review, we describe the diversity of intratumoural bacteria across 25 cancer types covering an extensive spectrum of analyzed intratumoural bacteria. Furthermore, the dual roles and mechanisms of their involvement in tumour progression and anticancer activity are summarized. Additionally, interventions and applications of engineered bacteria in cancer therapy, especially strategies used in clinical trials, are illustrated. This work describes the roles of intratumoural bacteria and their metabolic byproducts as regulators within the tumour microenvironment and highlights the potential translation of bacteria for cancer therapy.

© 2026 The Authors. Published by Elsevier B.V. on behalf of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

*Corresponding authors.
E-mail addresses: yuan_gao@fudan.edu.cn (Yuan Gao), xuyaozhang@fudan.edu.cn (Xuyao Zhang).

Peer review under the responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

https://doi.org/10.1016/j.apsb.2026.03.022
2211-3835 © 2026 The Authors. Published by Elsevier B.V. on behalf of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

As critical modulators, intratumoural bacteria have received widespread attention because of their function in cancer initiation, progression, and therapeutic response based on their ability to alter the balance of cell proliferation and apoptosis, and their immunological as well as metabolic interplay within the tumour microenvironment (TME)[1–4].

Recent advancements in high-resolution sequencing and spatially analytical metagenomics have facilitated the detection of microorganisms at tumour sites by measuring the DNA/RNA in the tumour tissue, which has revealed an unexpectedly high diversity of microbial communities across different tumour types[4,5]. The effects of intratumoural bacteria are also context-specific, with some bacteria promoting tumour growth and others inhibiting it. For example, in one study, the presence of *Bacteroides*, *Lactobacillus* and *Peptoniphilus* are linked to fewer tumour-infiltrating T lymphocytes that tested positive for CD4, CD8, and CD45RO in human pancreatic ductal adenocarcinoma (PDAC), where the bacterial niches are favourable for immune evasion[6]. *Clostridium perfringens* initiates epithelial-mesenchymal transition (EMT) and promotes oral squamous cell carcinoma metastasis[7]. Conversely, melanoma cells are colonized by the commensal bacteria *Lactobacillus reuteri* (*L. reuteri*), and one of the metabolites released by this bacterium increases anticancer immune responses and improves the effectiveness of immune checkpoint inhibitors (ICIs)[8]. The potential of intratumoural bacteria to serve as prognostic biomarkers has also been demonstrated. Intratumoural *Escherichia* has been linked to significantly longer overall survival (OS) in advanced non-small cell lung cancer patients treated with ICIs alone[9]. In contrast, high intratumour levels of *Fusobacterium nucleatum* (*F. nucleatum*) are associated with poor OS and progression-free survival in patients with cervical carcinoma[10]. Nevertheless, why these intratumoural bacteria play conflicting roles within tumours remains poorly understood. Despite this, microbial-driven therapeutic strategies, including leveraging intratumoural pathogenic bacteria or exogenously engineered bacteria, have also been widely explored. Over the past two decades, antibiotics and biological products such as bacteriophages have been demonstrated to selectively erase the cancer-promoting bacteria[11]. Meanwhile, lots of engineered bacteria such as programmable attenuated bacteria have been employed as cancer vaccines and drug delivery vehicles, due to their unique attributes including immunogenicity and precise tumour targeting ability[12].

Previous reviews have summarized intratumoural microorganisms in cancers and have focused on the origins of intratumoural bacteria as well as their role in tumour initiation, mechanisms of progression, and cancer immunotherapy[1,3,4,13,14]. Nevertheless, the roles of microorganisms within tumours are controversial, and their different prognostic values require further investigation. In this review, we summarize the history and diversity of the tumour microbiota across different tumour types. Moreover, we collect and identify 20 publications for analysis of the relative abundances of intratumoural bacteria (Supporting Information Fig. S1 and Table S1). Furthermore, the function and mechanisms of the impact of intratumoural bacteria on tumour biology as well as therapeutic strategies are illustrated. Finally, the current challenges and future directions are discussed, highlighting the possibility of bacteria-based cancer treatment.

2. Landmark events in the discovery of intratumoural bacteria

Over the past two centuries, microbial detection technologies have shaped our understanding of intratumoural bacteria (Fig. 1 and Supporting Information Fig. S2). As early as the 19th century, pioneers such as Robert Koch and Louis Pasteur reported the presence of bacteria at tumour sites[15]. In 1886, Doyen reported the identification of spherical *Micrococcus neoformans* in malignant tissues[16]. Controversially, Thomas Glover and Virginia Livingston-Wheeler (1990) reported that culturable bacteria exist in tumours, but their theories were later shown to be false[17,18]. In the same year, the US Food and Drug Administration approved intravesical *Bacillus Calmette-Guérin* (BCG) for the treatment of carcinoma *in situ* of the bladder[19]. Concurrently, clinical evidence revealed that the microbiome was linked to cancer: Wotherspoon's 1991 discovery of *Helicobacter pylori* (*H. pylori*) in 92% of gastric mucosa-linked lymphoid tissue lymphomas underscored the role of bacteria as oncogenic drivers[20]. Since 2006, large-scale initiatives—The Cancer Microbiome Atlas[21], The Cancer Genome Atlas, and the UK Biobank—have harmonized multi-omics data with microbial sequencing, revealing the spatial and taxonomic complexity of intratumoural bacteria[22]. These resources have allowed researchers to explore the contributions of microbes to tumour heterogeneity and therapy resistance.

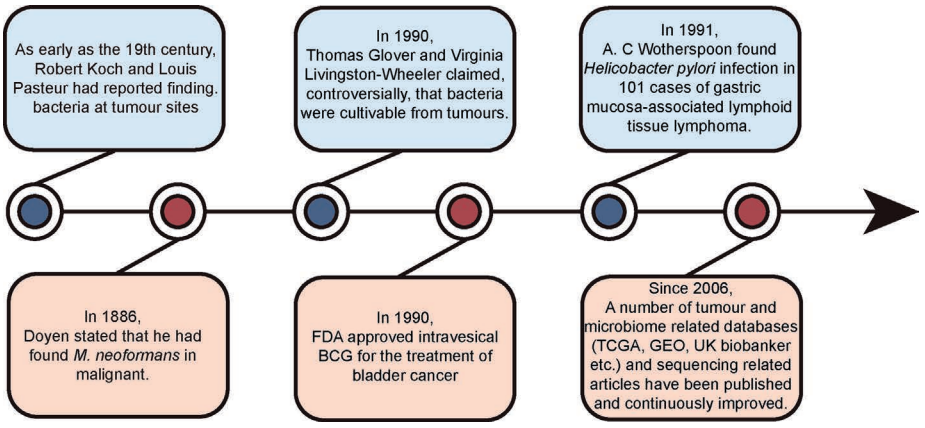

Figure 1 A milestone event for intratumoural bacteria discovery.

3. Characterization of bacteria in different tumours and their prognostic role

The intratumour microbes reported thus far typically enter tumours *via* three possible routes[23], which have been fully summarized in other reviews[3,13,24]: 1) from mucosal locations across the mucosal barrier of some organs, which have a cavity that is externally exposed; 2) from normal adjacent tissue; and 3) through haematogenous dissemination. Nevertheless, other studies have indicated that the intratumoural microbiota is likely an intrinsic and integral component of the TME rather than a secondary manifestation of pathogenic infections[3].

Moreover, high heterogeneity of intratumoural bacteria was reported, which was not only shaped by tumour molecular subtypes, spatial location, progression stage, genetic alterations, and the presence of multiple subclones, but also influenced by variations of angiogenesis, oxygen levels, microbial sources, endocytosis, and micropinocytosis[25,26]. To illustrate the diversity of intratumoural bacteria in various cancers, the primary bacterial genera or species found in several malignancies with a proportional quantity of bacteria across cancers at the genus level were analyzed according to the available data[27−45] (Fig. 2, Table 1, and Table S1). As shown in Fig. 2 and Table 1, intratumoural bacteria display spatial and temporal heterogeneity, which drives variability in chemotherapy efficacy, immune evasion, and mutation accumulation[46,47]. Therefore, the presence of intratumoural bacteria can predict tumour progression and therapeutic responses (Fig. 3).

3.1. Genitourinary cancers

3.1.1. Renal cell carcinoma (RCC)

In RCC, *Ochrobactrum* (21.23%), *Acinetobacter* (9.89%), and *Sediminibacterium* (6.77%) are the most frequently detected bacterial genera[33]. Among the three different subtypes of RCC, the most represented genera in clear cell RCC are *Cutibacterium* (10.90%), *Sphingomonas* (7.57%), and *Staphylococcus* (5.91%). In papillary RCC, the identified bacteria include *Cutibacterium* (13.52%), *Corynebacterium* (9.16%), *Escherichia−Shigella* (5.95%), and *Clavibacter* (5.41%). In chromophobe RCC, the most common genera are *Escherichia−Shigella* (14.28%), *Novosphingobium* (12.35%), *Cutibacterium* (9.22%), *Psychrobacter* (7.14%), and *Lactococcus* (5.44%)[34] (Fig. 2A). Four genera (*Colletotrichum*, *Leuconostoc*, *Gluconobacter*, and *Parabacteroides*) are associated with a poor prognosis, whereas three genera (*Cytobacillus*, *Alicyclobacillus*, and *Verrucomicrobium*) are associated with a favourable prognosis[49].

3.1.2. Bladder cancer

Paenibacillus, *Pseudomonas*, *Bacillus*, *Peptoclostridium*, *Acinetobacter*, *Brevibacillus*, *Corynebacterium*, *Prevotella*, *Azotobacter*, and *Actinoplanes* have been reported to be present in bladder cancer[50]. *Brachybacterium* and *Haloparvum* are much more abundant in muscle-invasive bladder cancer[51], whereas *Pseudomonas* (13.20%), *Staphylococcus* (6.52%), and *Mycobacterium* (6.04%) comprise the majority of the intratumoural bacteria in bladder urothelial carcinoma[52] (Table 1, Fig. 2B).

3.1.3. Prostate cancer

In prostate cancer, *Xanthomonas albilineans* GPE PC73, *Bradyrhizobium japonicum*, and *Methylobacterium radiotolerans* JCM 2831 are negatively correlated with tumour-node-metastasis stage, prostate-specific antigen level, and androgen receptor expression, respectively[53] (Fig. 3).

3.2. Gastrointestinal cancer

3.2.1. Colorectal cancer (CRC)

In CRC patients, *F. nucleatum*, *Streptococcus salivarius*, *Bacteroides*, and *Blautia* have been identified as the most prevalent species and genera[28,54]. The abundances of the genera *Fusobacterium*, *Bacteroides*, and *Escherichia−Shigella* were reported to be relatively high in samples from rectal cancer patients[29]. Moreover, tumour bacterial populations vary significantly between young-onset and elderly-onset CRC patients. While elderly-onset CRC patients exhibit higher abundances of *Bacillus*, *Staphylococcus*, *Listeria*, *Enterococcus*, *Pseudomonas*, *Fusobacterium*, and *Escherichia−Shigella*, the tumour bacteria of younger patients are more likely to be of the genera *Akkermansia* and *Bacteroides*[30] (Table 1, Fig. 2C).

In addition, the abundances of *Prevotella*, *Fusobacterium*, *Selenomonas*, *Fretibacterium*, *Porphyromonas*, *Peptostreptococcus*, *Leptotrichia*, and *Porphyromonas gingivalis* are correlated with short OS[55−57]. *Dialister*, *Casatella*, *F. nucleatum*, and *H. pylori* are linked to microsatellite instability, increased tumour immunity, and mutational burden[58−61]. Among them, *F. nucleatum* is associated with a poor outcome in CRC patients treated with oxaliplatin-based adjuvant chemotherapy[62,63]. However, a high *F. nucleatum* load is an independent positive sign among individuals with anal squamous carcinoma who undergo abdominoperineal resection[64] (Fig. 3).

3.2.2. Gastric cancer

Streptococcus, *Acinetobacter*, *Fusobacterium*, and *Brevundimonas* are the predominant intratumoural bacteria in gastric cancer[65−70]. Shao et al.[41] reported that *Prevotella* accounts for 23.3% of the total intratumoural bacteria in gastric cardia adenocarcinoma. Several common types of bacteria, including *Lactobacillus*, *Bacteroides*, *Mucispirillum*, *Parabacteroides*, *Enterococcus*, *Fusobacterium*, and *Prevotella*, are common in gastrointestinal stromal tumours[71] (Table 1, Fig. 2D). Moreover, *F. nucleatum* can serve as a prognostic marker of poor outcomes[72], and *H. pylori* is a strong biomarker for poor prognosis and low therapeutic efficacy in gastric cancer patients[73−76]. Additionally, a higher abundance of the *Klebsiella* genus has been linked to an improved OS probability in patients with gastric adenocarcinoma[77] (Fig. 3).

3.2.3. Oesophageal carcinoma

In oesophageal carcinoma, the abundances of *Fusobacteria*, *Lactobacillus*, *Proteobacteria*, *Negativicutes*, *Clostridia*, and *Leptotrichia* are linked to clinical characteristics[78,79]. High intratumoural concentrations of *F. nucleatum* are associated with poor recurrence-free survival (RFS)[80,81], while high *Streptococcus* levels enhance anti-programmed cell death protein 1 (anti-PD-1) treatment responsiveness and extend disease-free survival[82]. Recent 16S rRNA gene sequencing analyses reveal that the *Comamonas* (10%), *Parvimonas* (8.3%), *Gemmatimonas* (8.1%), and *Streptophyta* (5.4%) genera are predominant in oesophageal squamous carcinoma[35,41] (Fig. 2E). Additionally, the genera *TM7x*, *Sphingobacterium*, and *Prevotella* can serve as predictors of neoadjuvant therapy outcomes in patients with locally advanced oesophageal squamous cell carcinoma[83] (Fig. 3).

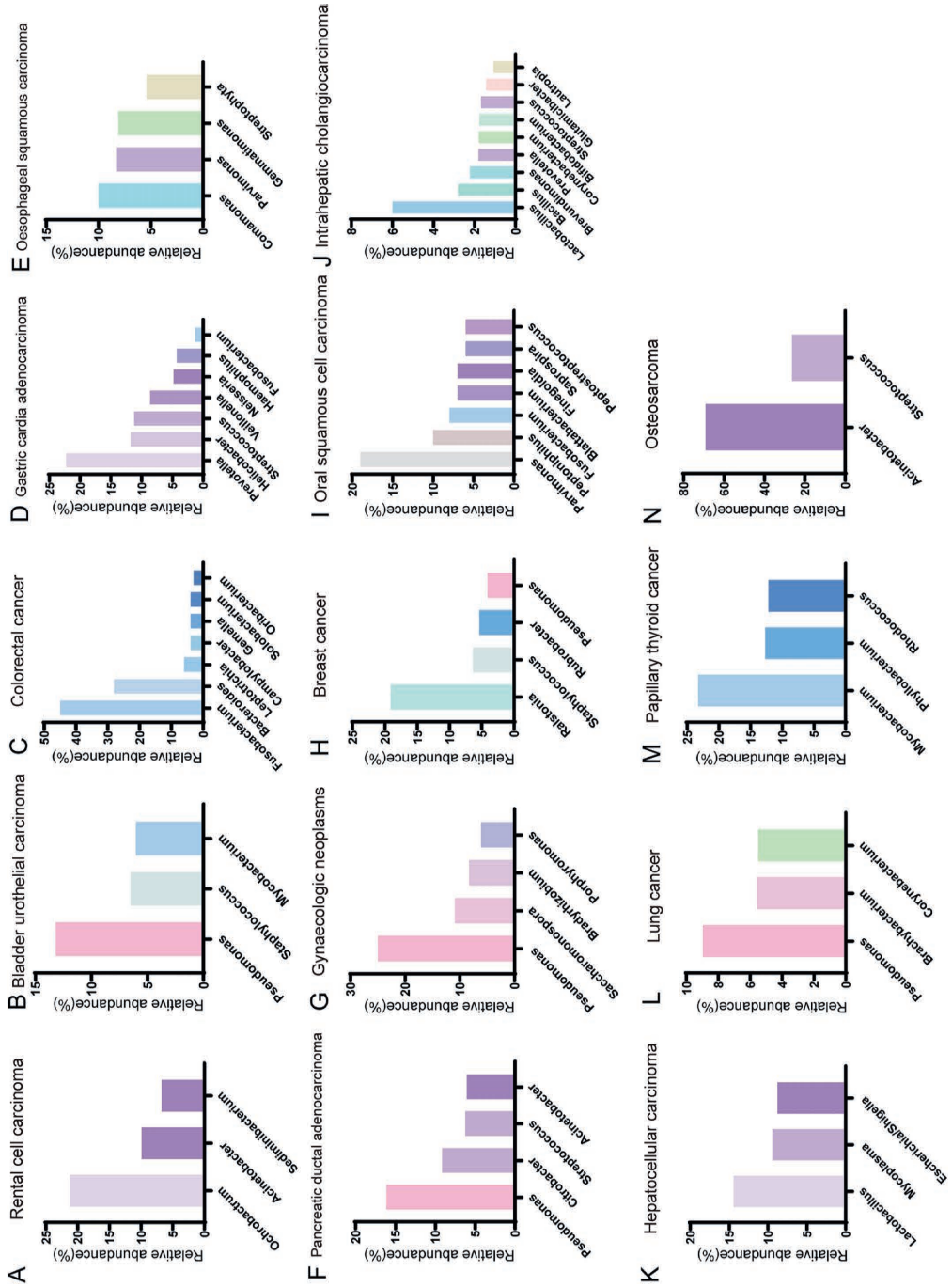

Figure 2 The intratumoural bacteria in 14 cancer types were summarized based on their relative abundances.

Table 1 The main intratumoural bacteria genera or species existing in 14 cancer types.

Bladder cancer	Colorectal cancer	Gastric cancer	Pancreatic cancer	Cervical cancer	Head and neck squamous cell carcinoma	Oral squamous cell carcinoma
Actinoplanes *Acinetobacter* *Azotobacter* *Bacillus* *Brachybacterium* *Brevibacillus* *Corynebacterium* *Haloparvum* *Paenibacillus* *Peptoclostridium* *Prevotella* *Pseudomonas*	*Acinetobacter* *Bacteroides* *Casatella* *Cupriavidus* *Dialister* *Fusobacterium* *Gemella* *Lachnoclostridium* *Lactococcus* *Leptotrichia* *Malassezia* *Oscillobacter* *Phocaeicola* *Porphyromonas* *Prevotella* *Roseburia* *Ruminococcus* *Sphingobium* *Sphingomonas* *Streptococcus*	*Acinetobacter* *Bacteroides* *Brevundimonas* *Burkholderia* *Enterococcus* *Escherichia/Shigella* *Fusobacterium* *Helicobacter* *Lactobacillus* *Methylobacterium* *Mucispirillum* *Oceanobacter* *Parabacteroides* *Prevotella* *Pseudomonas* *Streptococcus* *Syntrophomonas*	*Actinomyces* *Campylobacter* *Fusobacterium* *Granulicatella* *Haemophilus* *Prevotella* *Veilonella* *Pseudoxanthomonas* *Streptomyces* *Saccharopolyspora* *Acinetobacter* *Pseudomonas* *Porphyromonas* *Helicobacter*	*Pseudomonas* *Lactobacillus* *Bacteroides* *Ralstonia*	*Prevotella* *Fusobacterium* *Streptococcus* *Parvimonas* *Treponema*	*Porphyromonas* *Prevotella* *Fusobacterium* *Streptococcus* *Leptotrichia* *Haemophilus* *Rothia* *Capnocytophaga* *Campylobacter* *Neisseria*
Gingival squamous cell carcinoma	Nasopharyngeal carcinoma	Intrahepatic cholangiocarcinoma	Hepatocellular carcinoma	Lung cancer	Adenoid cystic carcinomas	Melanoma
Porphyromonas gingivalis, *Streptococcus gordonii*	*Corynebacterium* *Staphylococcus*	*Acidovorax* *Staphylococcus* *Bdellovibrio* *Roseimicrobium* *Roseburia*	*Escherichia-Shigella* *Methylobacterium* *Klebsiella* *Cutibacterium* *Acinetobacter* *Pseudomonas* *Ralstonia* *Stenotrophomonas* *Phyllobacterium* *Enterococcus* *Helicobacter*	*Pseudomonas* *Acinetobacter* *Sphingomonas* *Methylobacterium* *Enterobacter* *Propionibacterium* *Corynebacterium* *Micrococcus* *Streptococcus* *Staphylococcus*	*Neisseria* *Leptotrichia* *Actinomyces* *Streptococcus* *Rothia* *Veillonella*	*Fusobacterium* *Staphylococcus* *Paracoccus*

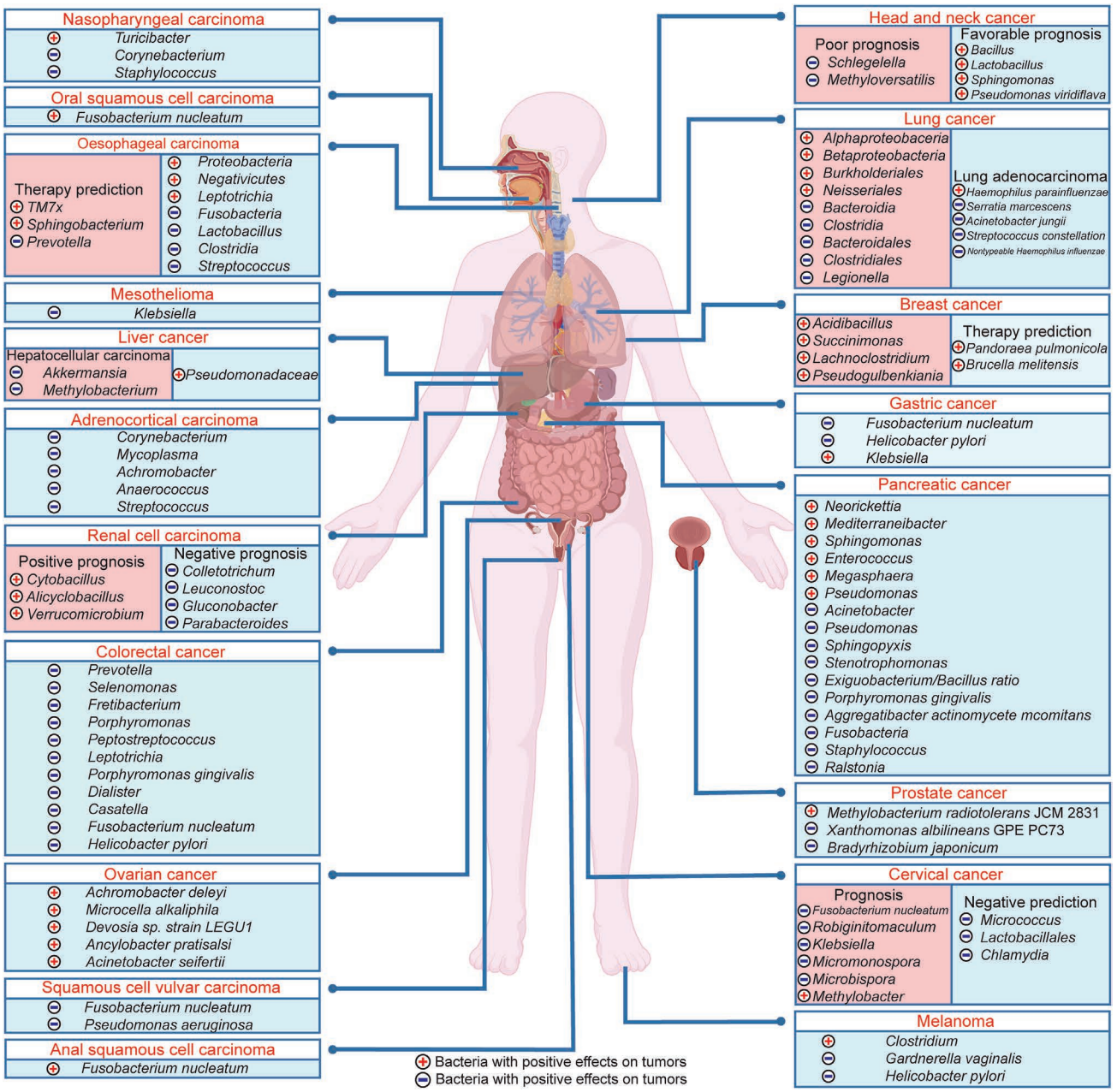

Figure 3 The summary of intratumoural bacteria with predictive value involves 19 types of cancer. Created with BioGDP.com [48].

3.2.4. *Pancreatic cancer*

Actinomyces, *Campylobacter*, *Fusobacterium*, *Granulicatella*, *Haemophilus*, *Prevotella*, *Veillonella*, *Pseudoxanthomonas*, *Streptomyces*, and *Saccharopolyspora* are identified through 16S RNA sequencing and internal transcribed spacer sequencing of pancreatic tumour samples[84–86]. Another study revealed that compared with healthy individuals, patients with pancreatic cancer exhibit a notably greater concentration of *Porphyromonas* according to 16S rRNA sequencing[87]. Moreover, samples from the pancreas, stomach, and duodenum of patients with pancreatic cancer contain the ribosomal DNA of *Helicobacter* species[88]. Among the species of microbes, *Escherichia coli* (*E. coli*), *Cutibacterium acnes*, *Methylobacterium radiotolerans*, *Achromobacter piechaudii*, and *Verminephrobacter eiseniae* have been identified in pancreatic cancer patients[89] (Table 1). In pancreatic tissue, elevated levels of *Acinetobacter*, *Pseudomonas*, *Sphingopyxis*, *Porphyromonas gingivalis*, and *Aggregatibacter actinomycetemcomitans* are strongly correlated with tumourigenesis[90,91], whereas *Fusobacterium* species may serve as prognostic biomarkers in this malignancy[92] (Fig. 3).

PDAC comprises approximately 90% of all pancreatic cancers[93]. *Pseudomonas* (16.12%), *Citrobacter* (9.13%), *Streptococcus* (6.26%), and *Acinetobacter* (6.06%) have been reported to be the predominant bacterial genera in PDAC[39] (Fig. 2F). Moreover, the presence of *Sphingomonas*, *Enterococcus*, *Megasphaera*, *Pseudomonas*, *Staphylococcus*, and *Ralstonia* in the tumours can predict the survival and prognosis of PDAC patients[94,95]. Lipopolysaccharides (LPS) produced mainly by gram-negative bacteria may negatively impact the efficacy of gemcitabine in advanced PDAC[96]. *Stenotrophomonas* and a high *Exiguobacterium*/*Bacillus*

ratio are associated with reduced survival of PDAC patients, whereas *Neorickettsia* and *Mediterraneibacter* are associated with extended survival[97,98].

In all gastrointestinal cancers, *Fusobacterium* is the most common bacterium, especially *F. nucleatum*. Therefore, the elimination of *Fusobacterium* from the digestive tract may alleviate cancer progression and drug resistance.

3.3. Gynaecologic neoplasms

In gynaecologic neoplasms, the top 10 most abundant genera account for 44.14%−52.12% of the total microbiome[27]. Determination of the relative abundance of bacteria has revealed that *Pseudomonas*, *Saccharomonospora*, *Bradyrhizobium*, and *Porphyromonas* are all present in the three most common gynaecological malignancies (cervical carcinoma, ovarian cancer, and endometrial cancer) (Fig. 2G). Among these genera, *Pseudomonas* is significantly more abundant in endometrial cancer than in cervical carcinoma. At the same time, *Bradyrhizobium* and *Saccharomonospora* are more prevalent in patients with ovarian cancer than in those with endometrial cancer. The abundance of *Lactobacillus* is markedly greater in patients with cervical carcinoma than in patients with endometrial cancer. At the same time, the *Porphyromonas* level is higher in patients with cervical carcinoma than in patients with both ovarian cancer and endometrial cancer[27,40,42]. Moreover, more bacterial species are present in ovarian cancer tissue than in adjacent normal tissue[99].

In cervical carcinoma, the predominant taxa of bacteria include *Pseudomonas*, *unidentified_Chlooroplast*, *Lactobacillus*, *Bacteroides*, and *Ralstonia*[100] (Table 1). *Robiginitomaculum*, *Methylobacter*, *Klebsiella*, *F. nucleatum*, *Micromonospora*, and *Microbispora* have prognostic value in patients with cervical carcinoma[10,101]. Among these, *Methylobacter* and *F. nucleatum* are negatively associated with mortality risk, and the other four are positively associated with mortality risk. The genera *Micrococcus* and *Lactobacillales* are associated with poor survival outcomes, whereas *Chlamydia* exhibits an even stronger negative correlation with OS[102−104]. Moreover, *F. nucleatum* and *Pseudomonas aeruginosa* have been identified as tumour-promoting bacteria in squamous cell vulvar cancer, and are linked to rapid tumour progression[105] (Fig. 3). Additionally, in terms of the relative abundance of bacteria in gynaecologic neoplasms, *Pseudomonas* is the most abundant type of bacteria (relative abundance ∼25%), as this genus is more than twice as abundant as other intratumoural bacterial genera (Fig. 2G).

3.4. Breast cancer

Ralstonia, *Rubrobacter*, *Lactobacillus*, *Streptococcus*, *Pseudomonas*, and *Staphylococcus* are the most dominant intratumoural bacteria in patients with breast cancer[32,106]. Among these, *Ralstonia* has the highest relative abundance, which is three times greater than that of the other bacteria (Fig. 2H). Moreover, the abundances of *Acidibacillus*, *Succinimonas*, *Lachnoclostridium*, and *Pseudogulbenkiania* have been reported to be positively associated with prognosis, immune gene expression, sensitivity to chemotherapy drugs, tumour-infiltrating immune cell abundance, and the effectiveness of immunotherapy in patients with breast cancer[107]. *Brucella melitensis* and *Pandoraea pulmonicola* have been identified as significant positive indicators of the response to neoadjuvant chemotherapy[108]. Furthermore, *Escherichia*, *Streptomyces*, *Clostridium*, *Ralstonia*, and *Salmonella* have been shown to reside in tumour epithelial cells in patients who achieve a nonpathological complete response[109] (Fig. 3). In addition, *Bacteroides*, *Alloprevotella*, and *Prevotella* are the dominant genera across $ER^-/HER2^+$, $ER^+/HER2^+$, and $ER^+/HER2^-$ tumours, whereas *Lactobacillus* is extremely prevalent in triple-negative breast cancer (TNBC)[31].

3.5. Head and neck cancer

Several varieties of head and neck cancers are known, including head and neck squamous cell carcinoma, gingival squamous cell carcinoma, oral squamous cell carcinoma, and nasopharyngeal carcinoma (NPC). *Schlegelella* and *Methyloversatilis* are typically found in the tumours of head and neck cancer patients with a poor prognosis. Additionally, patients with a good prognosis have high concentrations of *Bacillus*, *Lactobacillus*, *Sphingomonas*, and *Pseudomonas viridiflava*[110,111] (Table 1, Fig. 3).

3.5.1. Head and neck squamous cell carcinoma

Prevotella, *Fusobacterium*, *Streptococcus*, *Parvimonas*, and *Treponema* are shown to be elevated in head and neck squamous cell carcinoma tissues[112−115] (Table 1). Moreover, the abundance of *Fusobacterium* has been linked to a worse prognosis and a greater inflammatory impact. Compared with normal tissues, tumour tissues have a greater abundance of *Parvimonas*[113,114] (Fig. 3). Additionally, in laryngeal squamous cell carcinoma, the relative abundances of *Alloprevotella*, *Peptostreptococcus*, and *Porphyromonas* are strongly linked to an increased risk of nasopharyngeal recurrence[116] (Table 1).

3.5.2. Oral squamous cell carcinoma and gingival squamous cell carcinoma

The most dominant bacterial genera, *Parvimonas* (19%), *Peptoniphilus* (10%), *Fusobacterium* (8%), and *Finegoldia* (7%), are detected in data obtained from 10x Visium RNA-sequencing of oral squamous cell carcinoma[37]. High levels of *Porphyromonas*, *Prevotella*, *Fusobacterium*, *Streptococcus*, *Leptotrichia*, *Haemophilus*, *Rothia*, *Capnocytophaga*, *Campylobacter*, and *Neisseria* are identified by 16S rRNA sequencing and fluorescence *in situ* hybridization[117−119]. Moreover, *F. nucleatum*−associated oral squamous cell carcinoma is characterized by a distinct immune microenvironment, is observed primarily in elderly individuals with no alcohol consumption, and is correlated with a better prognosis[120] (Table 1, Fig. 2I). Moreover, *Porphyromonas gingivalis* and *Streptococcus gordonii* were reported in malignant oral epithelium, which indicates a possible link between these bacteria and gingival squamous cancer[121] (Table 1).

3.5.3. Nasopharyngeal carcinoma (NPC)

Bacteria present within NPC include *Sphingomonas*, *Burkholderia*, *Pseudomonas*, *Streptococcus*, *Corynebacterium*, and *Staphylococcus*[122,123]. The abundances of *Fusobacterium*, *Prevotella*, and *Porphyromonas* are greater in older NPC patients, the abundance of *Glutamicibacter* is greater in advanced-stage patients, and the abundance of *Pseudomonas* is greater in male patients[124]. In addition, *Turicibacter* has been identified as a possible independent prognostic predictor for NPC patients[125]. *Corynebacterium* and *Staphylococcus* have been linked to reduced disease-free survival and distant metastasis-free survival[122] (Table 1, Fig. 3).

The majority of head and neck cancers are squamous cell carcinomas. *Parvimonas* is shown to be highly abundant in head

and neck squamous cell carcinoma and oral squamous cell carcinoma, and could serve as a potential target for tumour treatment[126].

3.6. Liver cancer

It was reported that decreasing the prevalence of antitumour bacterial families and genera, such as *Pseudomonadaceae,* in tumour tissue could improve outcomes in patients with primary liver cancer[127] (Fig. 3). Intrahepatic cholangiocarcinoma (ICC) and hepatocellular carcinoma (HCC) are the two main types of liver cancer. In ICC, the most prevalent bacteria were reported at the genus level and include *Lactobacillus* (5.99%), *Bacillus* (2.81%), and *Brevundimonas* (2.22%)[128]. Moreover, *Rhodococcus*, *Ralstonia*, *Paraburkholderia*, *Pseudomonas*, *Thermomonas*, *Acinetobacter*, *Bacillus*, *Sphingomonas*, *Methylorubrum*, *Enterococcus*, and *Acidovorax* were reported to be the most common genera found in liver tumour tissue[129]. Shorter RFS and OS can be predicted by higher tumour microbial α diversity, which is also linked to lymph node metastases[36] (Table 1, Fig. 2J). In HCC, the predominant bacteria at the genus level are *Lactobacillus* (14.42%), *Mycoplasma* (9.44%) and *Escherichia—-Shigella* (8.87%)[43]. Another study reported that the genera *Helicobacter*, *Stenotrophomonas*, *Acinetobacter*, *Phyllobacterium*, and *Enterococcus* are most prevalent in HCC and that these bacteria may be associated with malignancy development[130,131]. Moreover, low levels of *Akkermansia* and *Methylobacterium* are associated with poor long-term outcomes in patients with HCC[132] (Table 1, Figs. 2K, and Fig. 3).

3.7. Lung cancer

The predominant bacteria at the genus level in lung cancer are *Brachybacterium* (5.56%), *Corynebacterium* (5.49%), and *Pseudomonas* (8.97%)[44] (Fig. 2L). Yang et al.[133] reported that numerous microbial genera, including *Blastomonas*, *Gemmatimonas*, *Mesorhizobium*, *Microbacterium*, *Mycobacterium*, *Mycoplasma*, *Parvimonas*, *Porphyromonas*, *Sphingomonas*, *Staphylococcus*, and *Veillonella*, are linked to the development of lung cancer (Fig. 3). Moreover, *Streptococcus* is found to predict survival in lung cancer[134]. In normal lung tissues, elevated levels of *Bacteroidia* (genus), *Clostridia* (genus), *Bacteroidales* (orders), and *Clostridiales* (orders) are shown to be associated with worse RFS, whereas greater quantities of *Alphaproteobacteria* (classes), *Betaproteobacteria* (classes), *Burkholderiales* (orders), and *Neisseriales* (orders) are shown to be linked with better RFS[135]. The genus *Thermus* is more abundant in tissues from patients with advanced-stage disease (stages IIIB and IV), whereas *Legionella* is more prevalent in patients who develop metastases[136] (Table 1, Fig. 3).

Furthermore, the most frequent genera in lung adenocarcinoma and squamous cell carcinoma are *Acinetobacter*, *Sphingomonas*, *Methylobacterium*, *Pseudomonas*, *Enterobacter*, *Propionibacterium*, *Micrococcus*, *Corynebacterium*, *Streptococcus*, and *Staphylococcus*[137]. Shi et al.[134] and Su et al.[138] reported that the abundances of *Streptococcus*, *Pseudoalteromonas*, *Luteibacter*, *Caldicellulosiruptor*, and *Serratia* are notably greater in lung adenocarcinoma patients. Four bacteria (*Serratia marcescens*, *Haemophilus parainfluenzae*, *Streptococcus constellation*, and *Acinetobacter jungii*) are found to have prognostic value. Of these, *Haemophilus parainfluenzae* is associated with positive two-year survival, while the other three are related to negative survival[139]. Nontypeable *Haemophilus influenzae* induces the expression of interleukin-17C (IL-17C) in the lungs, which may be a biomarker of poor prognosis[140] (Fig. 3).

3.8. Other types of cancer

The main bacterial genera in papillary thyroid carcinoma (PTC) include *Mycobacterium* (23.28%), *Phyllobacterium* (12.71%), and *Rhodococcus* (12.19%)[45] (Fig. 2M). Dysbiosis of the bacteria in specific types of PTC may account for the observed differences in PTC progression and pathogenesis[141,142]. In metastatic osteosarcoma, *Acinetobacter* (69.2%) and *Streptococcus* (26.3%) are the most important bacterial genera[38] (Fig. 2N). In adenoid cystic carcinomas, *Leptotrichia*, *Actinomyces*, *Neisseria*, *Streptococcus*, *Veillonella*, and *Rothia* are significantly elevated[143]. *Roseburia* and *Alloprevotella* are shown to be enriched in malignant tumours[144] (Table 1). In melanoma, the abundances of *Fusobacterium*, *Staphylococcus*, and *Paracoccus* were reported to be most strongly correlated with tumour progression[145]. While *Clostridium* is regarded as a protective factor, *Gardnerella vaginalis* and *H. pylori* are risk factors[146,147] (Fig. 3). In mesothelioma, the *Klebsiella* signature is shown to be more abundant in low-risk survivors[148]. Six genera (*Fusobacterium*, *Longibaculum*, *Intestinimonas*, *Pasteurella*, *Limosilactobacillus*, and *Arthrobacter*) are substantially more common in glioma cells than in nearby normal brain regions[149]. Additionally, *Corynebacterium*, *Mycoplasma*, *Achromobacter*, *Anaerococcus*, and *Streptococcus* are risk factors associated with OS in patients with adrenocortical carcinoma[150] (Fig. 3).

In summary, recent years have witnessed a surge in studies on the predictive significance of bacteria within tumours, revealing their potential to predict cancer stage and OS[1,151]. However, the significance of intratumoural bacteria is complex and context-dependent, as some bacteria enhance immune responses and improve survival outcomes in certain contexts[3]. The possibility of using intratumoural bacteria as prognostic biomarkers is highlighted by these findings, which also address the need for more studies to elucidate their functions and determine their role in cancer treatment by altering the tumour microbiota. Additionally, the knowledge of which tumour-associated bacteria are genuinely relevant to the function also needs further exploration.

4. The function and mechanism of intratumoural bacteria

Multiple facets of tumour biology, such as immune evasion, metabolic reprogramming, and TME regulation, are linked to the intricate interactions between bacteria and cancer growth[152–154]. As a result, the intratumoural bacteria and their metabolites modulate both positive and negative effects on tumour progression.

4.1. Tumour-promoting roles of intratumoural bacteria and their mechanism

Intratumoural and commensal bacteria are pivotal factors that shape cancer aggressiveness and act through pathways involving genetic mutation and modifications, immune evasion, activation of signalling pathways that promote tumour growth[155] (Fig. 4).

4.1.1. The impact of intratumoural microbes on tumour initiation and progression

4.1.1.1. Genetic mutation and modifications. Bacteria and their metabolites promote tumourigenesis by damaging

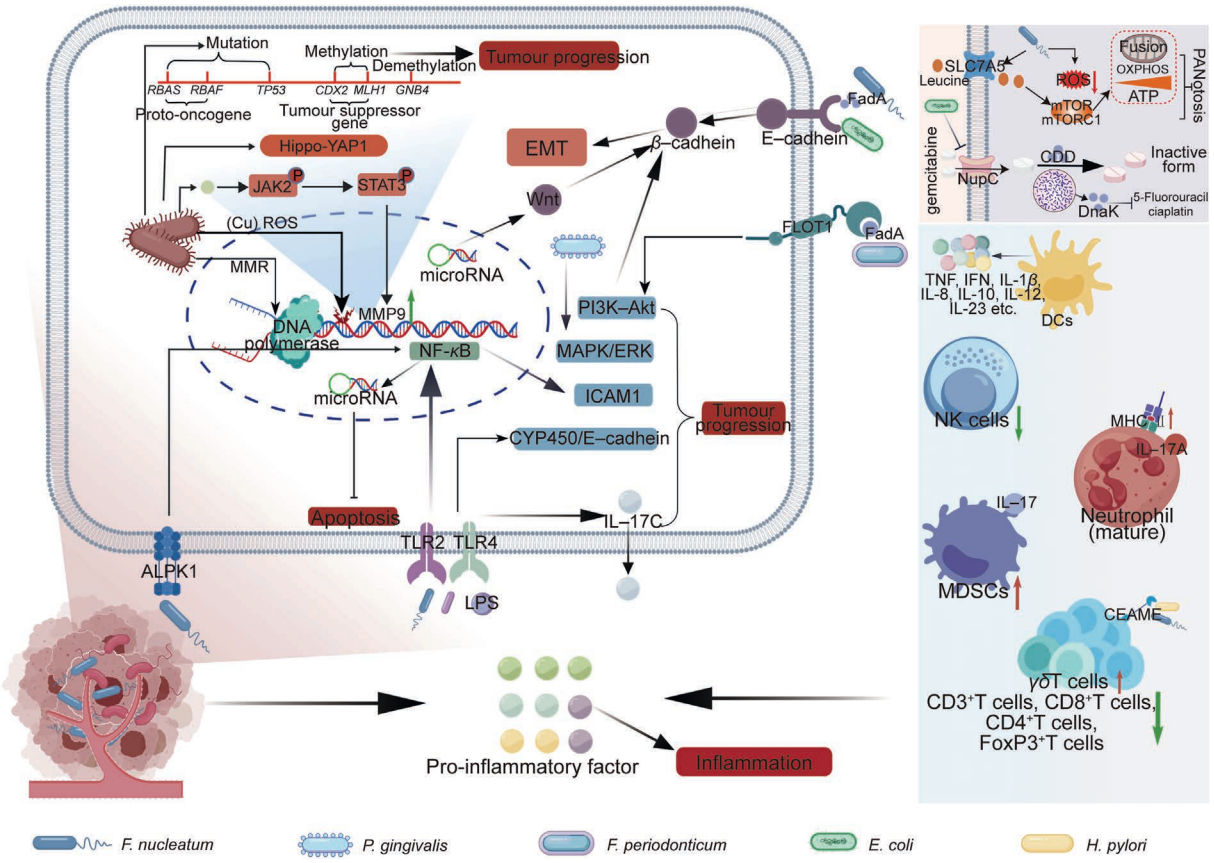

Figure 4 The mechanism by which bacteria promote cancer progression. Bacteria affect genetic status to cause cancer, including by mutating proto-oncogenes and tumour suppressor genes, increasing the burden on tumours through gene demethylation, influencing tumour mismatch repair, promoting gene damage through the synthesis of reactive oxygen species (ROS); Bacteria regulate the cancer immune microenvironment by binding to receptors such as Alpha kinase 1, Toll-like receptor (TLR), Flotillin 1, and E-cadherin to activate related pathways; Bacteria promote the secretion of inflammatory factors, thereby promoting tumour progression and inhibiting tumour apoptosis; Some bacteria enhance drug tolerance by metabolizing drugs (Gemcitabine, 5-Fluorouracil, and Cisplatin) and inhibiting pathways that drug enter intracellular; Leucine secreted by bacteria could also inhibit PANotosis. Created with BioGDP.com [48].

genes[156–158]. For example, *pks*$^{+}$ *E. coli* and enterotoxigenic *Bacteroides fragilis* encode and secrete carcinogenic toxins that induce DNA damage, which results in faster tumour onset and greater mortality[156]. *F. nucleatum* is strongly linked to mutations in the proto-oncogenes *KRAS* and *BRAF*[159,160], and *Acidovorax* and *Massilia* are enriched in *TP53*−mutated tumours in lung cancer, especially in squamous cell carcinoma[161,162]. Meanwhile, *F. nucleatum* causes DNA damage and promotes oral cancer cell growth through the Ku70/p53 pathway[163]. Moreover, *Bacteroides fragilis* and *F. nucleatum* increase ROS levels and DNA damage in breast cancer and CRC models[164–166], and macrocyclic colibactin causes copper-mediated oxidative cleavage, which results in DNA double-strand breaks in colon tumours[167].

Furthermore, some studies have reported that intratumoural bacteria directly regulate host epigenetic modifications. For example, a mutual mediation effect between the intratumoural bacteria and host DNA methylation variations is identified in stomach adenocarcinoma[74]. Subsequently, *Hungatella hathewayi* and *F. nucleatum* mediate epigenetic modification of the host epigenome through upregulation of DNA methyltransferases, thus promoting hypermethylation and silencing of tumour-suppressor genes like *CDX2* and *MLH1* in CRC[159,160]. Besides, an *E. coli* effector protein−EspF and *H. pylori* can modulate the DNA mismatch repair pathway in CRC and gastric cancer models[168–170], and the induction of aberrant DNA methylation is the main pathway involved in *H. pylori* infection-mediated gastric adenocarcinoma[171,172].

4.1.1.2. Activation of signalling pathways that promote tumour growth. Intratumoural bacteria activate cancer progression and metastasis signalling pathways. The intratumour *Campylobacter* production of genotoxin triggers JAK2/STAT3/MMP9 signalling pathway, which promotes CRC metastasis[173]. By triggering the Hippo−YAP1 pathway, *H. pylori*-induced aberrant demethylation and overexpression of GNB4, which promotes the development of gastric cancer[171]. Similarly, enterotoxin from *Clostridium perfringens* suppresses the phosphorylation of YAP1 and promotes YAP1 nuclear translocation, causing oral squamous cell carcinoma progression[7]. During EMT, the E-cadherin/*β*-catenin complex is downregulated. Through their modulation of the E-cadherin/*β*-catenin signalling pathway, *E. coli* and FadA in *F. nucleatum* may promote the spread of cancer[174,175]. Moreover, CRC cells infected with *F. nucleatum* facilitate tumour metastasis by selectively harbouring *miR-1246*, *miR-92b-3p*, and *miR-27a-3p*, which target GSK3*β* and activate the Wnt/*β*-catenin pathway[176]. Similarly, through FadAL adhesin-mediated Flotillin

1 binding and palmitic acid accumulation, *F. periodonticum* enhances Wnt3A palmitoylation, which induces hyperactivation of Wnt/β-catenin signalling to drive EMT and therapeutic resistance[177]. Furthermore, *P. gingivalis,* an anaerobic bacterium, promotes Akt-mediated tumour progression in pancreatic cancer[178]. 5-Fluorouracil-resistance in CRC is enhanced by butyrate generated from the intratumour microbiota. This resistance is attributed to the PI3K−AKT signalling pathway activated by butyrate[179]. Additionally, intracellular *P. gingivalis* increases the growth of CRC cells by activating MAPK/ERK signalling. Similarly, *F. nucleatum* activates the MAPK signalling pathway in breast cancer [180,181].

Inflammation can also promote tumour progression. When the tumour immune environment is modified, bacteria within tumours increase the release of several inflammatory factors, such as tumour necrosis factor (TNF), interferon (IFN), IL-6, IL-8, IL-10, IL-12, IL-17, IL-23, and IL-1β[182−187]. NF-κB is an important mechanism through which intratumoural bacteria promote inflammation. In HCC, *Stenotrophomonas maltophilia* causes a senescence-associated secretory phenotype in hepatic stellate cells *via* TLR4/NF-κB-dependent NLRP3 inflammasome activation, which results in the release of protumourigenic inflammatory mediators that accelerate cancer progression[131]. Meanwhile, lactate overproduction by *E. coli* triggers RIG-I lactylation, blunting NF-κB-dependent transcription of *Nlrp3* in macrophages. This suppression of inflammasome activity locked macrophages into an M2 state, fostering immune tolerance and metastatic outgrowth[188]. Furthermore, *F. nucleatum* activates ALPK1/NF-κB/ICAM1 signalling, which increases CRC cell adherence to endothelial cells and promotes tumour metastasis[189]. In prostate epithelial cells, the NF-κB and STAT3 transcription factor-related pathways constitute key pathways involved in tumourigenesis. Both protumoural myeloid cell infiltration triggered by *Bacteroides fragilis* toxin and the production of cytokines or chemokines such as IL-6 and IL-8 induced by *Propionibacterium acnes* are induced by NF-κB and STAT3-related pathways[190,191]. Through the activation of IL17/NF-κB/RelB signalling, *F. nucleatum* recruits tumour-associated neutrophils to increase the growth of gastric cancer and immune evasion[192]. As we know, TLRs, which function as pattern−recognition receptors, significantly contribute to the immune therapy evasion of tumours by bacteria, especially by those that express TLR2 and TLR4[193]. It was reported that extracellular vehicles (EVs) of *F. nucleatum* promote tumour development and metastasis in patients with breast cancer *via* TLR4[194]. Moreover, *F. nucleatum* activates the cytochrome P450/epoxyoctadecenoic acid axis through the TLR4/Keap1/NRF2 signalling pathway. Meanwhile, *F. nucleatum* targets certain microRNAs and the innate immune signalling pathways MYD88 and TLR4 to alter the autophagy process in CRC[195−197]. TLRs also play a role in cytokine secretion. *S. choleraesuis* markedly increases the production of IFN-γ, as well as the IFN-inducible chemokines CXCL9 and CXCL10, *via* TLR4 activation[198] (Fig. 4). Concurrently, *Propionibacterium acnes* promotes epithelial ovarian cancer progression by activating the Hedgehog signalling cascade, which triggers TNF-α, IL-1β, and IL-6 production, promoting a cytokine-rich niche that enhances cancer cell invasion and proliferation[199]. Additionally, *F. nucleatum*-Dps promotes CRC metastasis *via* CCL2/CCL7-induced Hedgehog signalling[200].

4.1.1.3. Stimulation of immune-evasive pathways. Persistent immune homeostasis depends on the cross-interaction between bacteria and their host. Intratumoural bacteria can evade the immune response and affect tumourigenesis by promoting an immunosuppressive TME and immune cell inactivation[13].

Bacteria promote the secretion of inflammatory factors and immune escape through bacteria themselves and their secretions, including major *H. pylori* virulence factors (*e.g.*, CagA, VacA, BabA, and SabA) and other outer membrane proteins (neutrophil-activating protein and gamma-glutamyl transpeptidase)[201]. Besides this, *S. multivorum* was reported to encourage tumour cells to release the chemokines CCL20 and CXCL8. Tumour immune escape is promoted by CCL20 released in the TME, which decreases $CD8^+$ T cell invasion and promotes the recruitment of Treg cells[202]. *F. nucleatum* infection induces both normal pancreatic epithelial cells and PDAC cells to secrete increased amounts of the cytokines GM-CSF, CXCL1, IL-8, and MIP-3α. GM-CSF/IL-8-driven paracrine network dampened $CD8^+$ T cell activity in pancreatic cancer[203−205]. Moreover, commensal bacteria trigger Myd88-dependent production of IL-1β and IL-23, which drive the activation of $\gamma\delta$T cells, and the subsequent release of cytotoxic effectors such as IL-17 to promote an inflammatory immunosuppressive environment in the lung tumour model[206].

Furthermore, intratumoural bacteria exert an inhibitory effect on immune cells. *H. pylori* and *F. nucleatum* attenuate antitumour immune responses by engaging CEACAM1, an inhibitory receptor that is mostly produced by natural killer (NK) cells and activated T cells[207−209]. *F. nucleatum* regulates the tumour immune microenvironment by selectively aggregating tumour-infiltrating myeloid cells, including $CD11b^+$ myeloid cells, myeloid-derived suppressor cells (MDSCs), tumour-associated macrophages (TAMs), classical myeloid dendritic cells (DCs), and $CD103^+$ regulatory DCs, thereby potentiating tumourigenesis[210]. Similarly, *Cidovorax temperans* alter neutrophil maturation and induce polarization of helper T cell 17 cells, thereby contributing to the development of lung cancer[211,212]. Sequentially, *F. nucleatum* promotes the growth of oral squamous cell carcinoma by enhancing lactate production *via* GLUT1[213]; the lactate receptor HCAR1 facilitates the attraction of immunosuppressive PMN−MDSCs and TAMs[214]. The recruitment of MDSCs is linked with a notable reduction in the numbers of $CD3^+$ T cells, $CD4^+$ T cells, $CD8^+$ T cells, and $FoxP3^+$ T cells, as well as a decrease in peritumoural tertiary lymphoid structures and M1 macrophage differentiation in CRC[210,215−218]. Another study reported that *F. nucleatum* exploited multiple mechanisms to subvert immune surveillance: its Fap2 protein inhibited TIGIT-expressing tumour-infiltrating lymphocytes, while recruitment of MDSCs *via* CXCL1 autocrine signalling in pancreatic cancer[203−205]. Besides, some bacterial metabolites also promote immune cell inactivation. For example, microbiota-derived butyrate increases expression of H19 in lung cancer cells through inhibiting *HDAC2* and increasing *H3K27* acetylation at the H19 promoter, and induces M2 macrophage polarization[219]. Tryptophan-derived indole compounds generated by *Lactobacillus* can activate immunosuppressive TAMs *via* aryl hydrocarbon receptor signalling, leading to impaired antitumour $CD8^+$ T cell responses in PDAC mouse models[220].

4.1.2. The influence of intratumoural bacteria on therapeutic response and treatment efficacy

Intratumoural bacteria exert a protective effect on tumours through metabolism and the absorption of drugs, which may cause

therapeutic resistance[221]. Gammaproteobacteria exemplify this metabolic warfare: their expression of cytidine deaminase converts gemcitabine—a frontline chemotherapeutic—into its inactive metabolite, 2',2'-difluorodeoxyuridine, which effectively disarms this drug in pancreatic and colorectal malignancies[39,222,223]. *E. coli* upregulates the nucleoside permease NupC to sequester gemcitabine within bacterial cells, thereby reducing its bioavailability and decreasing its therapeutic efficacy in cocultured tumours[224].

Moreover, bacteria promote tumour drug resistance by influencing the target sites of drugs. *N*-(3-Oxo-dodecanoyl) homoserine lactone, a quorum-sensing signalling molecule secreted by *Pseudomonas aeruginosa*, induces TGF-β signalling, triggers ErbB2 phosphorylation and its downstream target activation, and overcomes the inhibitory effect of trastuzumab on ErbB2 in breast cancer[225]. *F. nucleatum* exploits host stress responses by activating bacterial DnaK chaperones, which stabilize and enhance cancer cell DNA repair pathways. This intervention counteracts cisplatin- and 5-fluorouracil-induced DNA damage, enabling tumour cells to evade apoptosis[226]. Moreover, *F. nucleatum* orchestrates radioresistance in NPC by hijacking nutrient-sensing pathways *via* the following mechanism: the SLC7A5 transporter shunts leucine into the mTORC1 signalling pathway, which suppresses PANoptosis—a coordinated cell death program triggered by radiation—and fosters tumour cell survival[227] (Fig. 4).

4.2. *Anti-tumour roles of intratumoural bacteria and their mechanism*

Emerging evidence highlights the capacity of intratumoural bacteria and their metabolic byproducts to enhance antitumour activity *via* various mechanisms, including metabolism regulation, programmed cell death, stimulating STING signalling, inhibiting PD-1/PD-L1, and enhancing immune activity, etc. (Fig. 5).

Bacteria induce the programmed cell death of tumour cells, including apoptosis and pyroptosis[228]. In HCC, Hpn, a protein released by *H. pylori*, suppresses USP5 expression and activates P14—P53 signalling, both of which contribute to apoptosis[229]. Butyrate, a product of *Clostridium butyricum*, triggers superoxidative stress and intracellular lipid accumulation, increasing the vulnerability of PDAC to ferroptosis[230] (Fig. 5A). In TNBC, microbial-derived TMAO induces tumour cell pyroptosis, a type of controlled cell death in which damage-associated molecular patterns (DAMPs) are released. These DAMPs activate $CD8^+$ T cells, whose cytotoxic function is further potentiated by commensal microbiota, suggesting a synergistic interplay between microbial metabolites and resident flora in enhancing immunotherapy efficacy[231].

Moreover, the STING signalling pathway plays an essential part in the innate immune response. *Bifidobacterium* converts the immune responder for anti-CD47 immunotherapy in a STING and

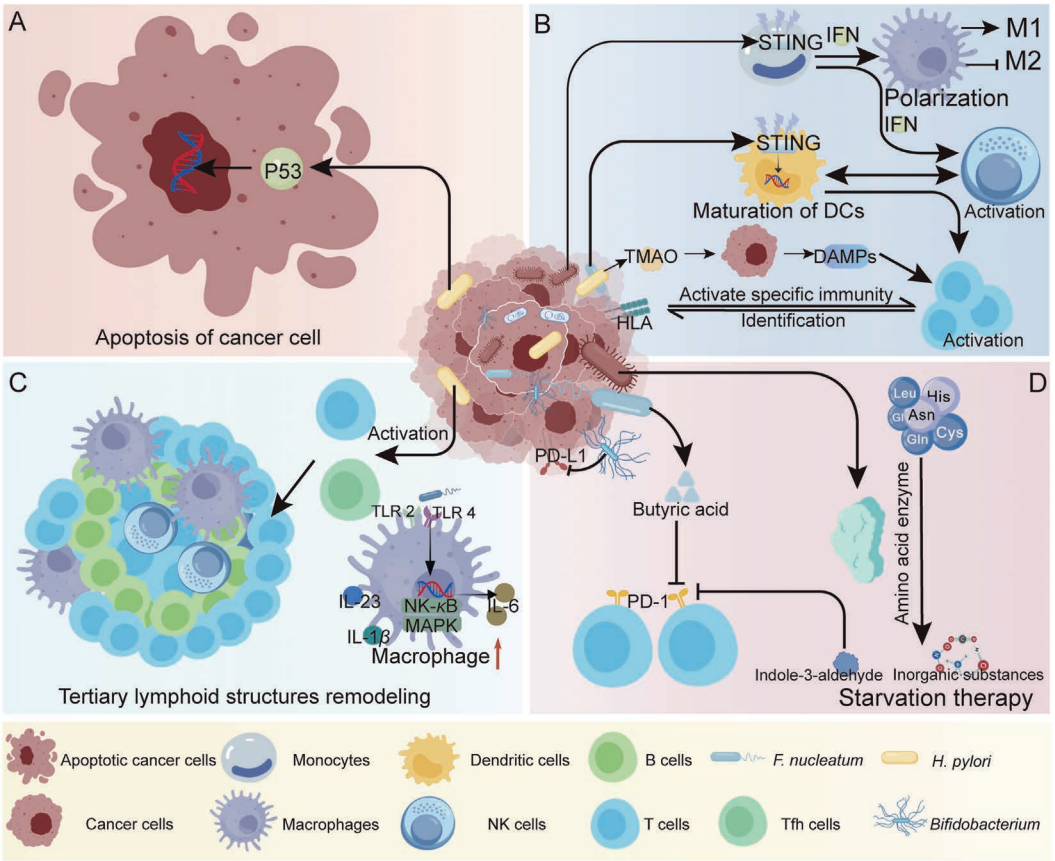

Figure 5 The role of bacteria in cancer therapy. (A) *H. pylori* activates the P14—P53 signal, stimulating cell apoptosis in HCC. (B) Bacteria trigger STING signal and activate specific immunity; Microbial-derived trimethylamine *N*-oxide (TMAO) induces tumour cell pyroptosis; Tumour bacteria are displayed by human leukocyte antigen (HLA) molecules in tumour cells. (C) Peritumoural tertiary lymphoid structures are enlarged by tumour-adjacent lymphoid structures and T follicular helper cells specialized to bacteria. (D) Microbial secretions or bacteria inhibit ICIs; Microbial enzymes are used in amino acid deprivation therapy. Created with BioGDP.com[48].

IFN-dependent model. Intratumoural bacteria-derived STING agonists induce IFN-I production by intratumoural monocytes to regulate macrophage polarization and NK cell−DCs crosstalk[232,233]. Interestingly, intracellular bacteria activate bacterial-specific immunity, which was reported in 41 distinct species of intracellular bacteria, displayed by HLA class I and II molecules in tumour cells, promoting antigen presentation, thereby triggering immune responses in melanoma[234] (Fig. 5B).

Furthermore, bacteria inhibit the expression of PD-1/PD-L1 and promote the infiltration of tumour immune cells. In microsatellite-stable CRC, *F. nucleatum*-derived butyrate suppresses histone deacetylase 3/8 activity in $CD8^+$ T cells. This epigenetic reprogramming drove *H3K27* acetylation at the *Tbx21* promoter, transcriptionally repressing PD-1. Similarly, his receptor PD-L1 could be inhibited by *Bifidobacterium* in melanoma. *F. nucleatum*-driven $CX3CR1^+$ $PD\text{-}L1^+$ phagocytes routed to CRC tissues and reshaped TME[235]. By alleviating PD-1/PD-L1-mediated inhibition, bacteria such as *F. nucleatum* and *Bifidobacterium* enhance T cell proliferation and activation, enabling sustained immune responses to tumour[236−238].

In addition, tumour bacteria link other cellular programs and immunity, including NK/T cells and effector T cells activation in pancreatic cancer[234]. Spatiotemporal modulation of immune cell trafficking is exemplified by *Clostridia* in bile tract cancers. By recruiting MDSCs and activating the PI3K−CCL2−CCR2 pathway, *Clostridium* alters the TME to improve $CD8^+$ T lymphocyte infiltration, a crucial component of antitumour immunity[239]. Other ways bacteria activate immunity[240,241], such as: mediating bacteria-specific T follicular helper cells and tumour-adjacent lymphoid structures, and expanding peritumoural tertiary lymphoid structures, which in turn promote anti-tumour immunity[242]. TLR2/4 and MyD88 signalling pathways are required for optimal NF-κB and MAPK activation in macrophages in response to *F. nucleatum* and *A. actinomycetemcomitans*[243] (Fig. 5C).

Interestingly, the intratumoural bacteria inhibit tumour progression by metabolizing amino acids. In melanoma, *L. reuteri* colonizes tumour niches and metabolizes dietary tryptophan into indole-3-aldehyde. This metabolite drives localized expansion of IFN-γ-producing $CD8^+$ T cells, synergizing with ICIs to overcome immunosuppressive barriers[8]. Tumour expansion reduces the expression of certain enzymes (*e.g.*, microbial L-asparaginase), causing auxotrophy for specific amino acids. Tumour development is specifically hindered by this decrease because normal cells produce these amino acids *via* regular routes[244] (Fig. 5D).

Overall, intratumoural bacteria and their metabolic byproducts amplify anti-tumour activity through various mechanisms. Understanding these mechanisms will help expand existing therapeutic regimens for cancer therapy.

5. Treatment opportunities

5.1. Elimination of tumour-promoting bacteria

To overcome microbial-driven impact, innovative strategies have been developed to selectively eliminate intratumoural pathogenic bacteria, thereby sensitizing tumours to conventional therapies.

5.1.1. Antibiotic-based therapy

Conventional antibiotics are used in conjunction with antitumour medications to disrupt bacteria-driven therapy resistance, which further increases tumour cell death (Table 2). For example, metronidazole reverses *F. nucleatum*-induced EMT during liver metastasis and improves the efficacy of oxaliplatin in a CRC model[245]. Similarly, co-delivery of ferritin-caged doxorubicin with metronidazole highly resensitizes breast cancer to PD-L1 therapy[246], and metronidazole is covalently linked to fluorouridine to form a conjugate through which a synergistic cytotoxic effect is achieved in a CRC model[247]. Moreover, the concurrent use of ampicillin to deplete *Staphylococcus epidermidis* enhances outcomes in breast cancer patients treated with paclitaxel[248]. Further, colistin-crosslinked gemcitabine or doxycycline nanoparticles (NPs) have been used to eliminate *F. nucleatum* and *E. coli* in breast cancer[249,250]. Additionally, doxycycline is co-delivered with doxorubicin to prevent cancer metastasis by controlling the abundance of intratumoural *Staphylococcus* and *Lactobacillus* in TNBC[251]. Other antibiotic complexes such as silver-tinidazole allow the targeted eradication of tumour-associated *F. nucleatum* in both primary and metastatic CRC lesions without disrupting the gut microbiota[252].

Notably, antibiotic-based combined therapy for cancer treatment has already undergone clinical trials (Supporting Information Table S2). For example, aztreonam and vancomycin, in combination with pembrolizumab for the treatment of right-sided colon cancer and colon adenoma, are tested in a phase II clinical trial (NCT04312360) with promising results. In a phase II study, metronidazole or chlorhexidine was demonstrated to regulate the inflammation caused by intratumoural bacteria in head and neck squamous cell carcinoma (NCT06627270).

5.1.2. Biological products and other antimicrobial substances

Biological products redefine bacterial eradication in tumours and surpass traditional antibiotics (Table 3). Magnetic nanocatalytic agents exemplify this innovative therapy: in CRC, arginyl-glycyl-aspartic acid and 3-carboxypropyl triphenylphosphonium surface-modified particles generate localized hydroxyl radicals *via* Fenton reactions under alternating magnetic fields, which leads to the selective disintegration of *F. nucleatum* and the induction of DCs maturation, while healthy tissue is spared[253]. Concurrently,

Table 2 The strategic integration of traditional antibiotics with antineoplastic agents.

Antibacterial substance	Drug delivery system	Ref.
Metronidazole	Metronidazole and oxaliplatin were encapsulated within poly (lactic-co-glycolic acid) NPs.	245
Metronidazole	Doxorubicin coloaded into a nanovehicle was ferritin-nanocaged.	246
Metronidazole	Metronidazole−fluorouridine NPs.	247
Ampicillin	Oral ampicillin and paclitaxel	248
Colistin	Colistin and doxycycline loaded into *F. nucleatum*-mimicking nanovehicles.	249
Colistin	Colistin crosslinked gemcitabine micelle.	250
Doxycycline	Doxycycline and doxorubicin were combined to create a multifunctional nanoplatform.	251
Silver-tinidazole	A silver-tinidazole complex encapsulated in liposomes.	252

Table 3 Biological products and other substances that remove bacteria.

Antibacterial substance	Drug delivery system	Ref.
Amino acid	A monodispersed, superparamagnetic nanocatalytic drug was created by combining 3-carboxypropyl triphenylphosphonium bromide with arginyl-glycyl-aspartic acid.	253
Lactobacillus rhamnosus GG	Gallium polyphenol network-equipped *Lactobacillus rhamnosus* GG probiotics.	254
Antibody	Mesoporous silica NPs functionalized with bacterial lipoteichoic acid antibodies for targeted delivery to bacteria.	255
Anti-TNFα	The anti-TNFα medication was accommodated, and Au NPs were anchored using Nb_2C nanosheets to create the composite.	256
Antibody	A light-responsive hydrogel was composed of a hyaluronic acid-coated microshell and a core modified by bacteria-targeting LPS antibody and heat-responsive plate.	257
Nanozyme	A new protein-supported copper single-atom nanozyme was created, utilizing metal elements as the active core.	258
LL37	A human antimicrobial peptide was produced *in situ* by cancer-associated fibroblasts using an optogenetic technology.	259
Bacteriophages	Targeting *Enterococcus hirae* phage.	261
Bacteriophages	Targeting *E. coli* phage.	262
Silver	Epirubicin was loaded into the mesopores of dendritic mesoporous silica NPs to form the antibacterial-antineoplastic NPs.	263
Vermiculite/copper telluride	Vermiculite/copper telluride bio-heterojunctions.	264
D-Penicillamine	Chelating the copper chelator D-penicillamine with Zn^{2+}.	265
Ellagic acid	Ellagic acid-protein nano-complex.	266
Allicin	Glucose oxidase and allicin co-loaded into an acid-stable adhesive hydrogel.	267
Lauric acid	A nanodrug delivered the platinum prodrug and antimicrobial lauric acid.	268
Tellurium	An oral dose form of tellurium-containing NPs loaded with cisplatin.	269
Berberine	A double-bundle DNA tetrahedron-based nanocarrier was created to deliver berberine to intratumoural bacteria.	270

metabolic interference strategies involve the use of engineered probiotics such as *Lactobacillus rhamnosus* GG coated with gallium−polyphenol networks, which disrupt iron respiration in tumour-promoting *Proteobacteria* and neutralize microbiota-derived LPS, resensitizing pancreatic tumours to immunotherapy[254]. Targeted drug delivery is also achieved through bacteria-specific nanocarriers. In a breast cancer model, mesoporous silica NPs decorated with lipoteichoic acid antibodies can target *Peptostreptococcus anaerobius* and deliver irinotecan to kill tumours[255]. Multimodal phototherapy platforms, such as Nb_2C/Au nanocomposites, disrupt *E. coli* and *Staphylococcus aureus* metabolism *via* photothermal effects while generating immunogenic microbial neoantigens that prime tumour-specific $CD8^+$ T cells in CRC and breast cancer models[256]. In osteosarcoma, light-responsive hydrogels containing nanomicrostructures trigger bacterial LPS, which upregulates the expression of CD4 and CD8[257]. In a CRC model, the novel copper single-atom nanozyme BSA−Cu SAN generates ROS and reduces glutathione levels, which effectively scavenge pathogen-tumour symbionts such as *F. nucleatum*[258]. The human antibacterial peptide LL37 is generated by engineering cancer-associated fibroblasts *in situ* to eliminate *F. nucleatum* while also encoding an *HSP* gene to reduce breast cancer volume[259].

Furthermore, bacteriophages are exploited as antibiofilm agents and antimicrobial adjuvants while rarely inducing bacterial resistance, making them an invaluable asset in the era of antibiotic resistance[260]. Bacteriophages can be used to encapsulate antitumour drugs or to eliminate intratumoural bacteria directly. For example, a phage strain isolated from human saliva that can specifically lysed *F. nucleatum* can be engineered to deliver irinotecan to CRC[11]. Targeting *Enterococcus hirae* phage activates MHC-restricted antigens, enhancing cyclophosphamide or anti-PD-1 efficacy[261]. Moreover, bacteriophages that target *E. coli* have been used to deliver PD-1[262].

Other antimicrobial strategies, such as the combination of antibacterial silver NPs and epirubicin, result in *F. nucleatum* eradication and CRC apoptosis[263]. Vermiculite/copper telluride bio-heterojunctions generate substantial amounts of ROS *via* photodynamic/chemodynamic activation, which effectively scavenges *E. coli* within CRC cells and initiates autophagy in tumour cells[264]. Moreover, natural compounds such as ellagic acid, berberine, and D-penicillamine have been repurposed into tumour-targeted NPs, as they selectively deplete intratumoural *F. nucleatum*, *E. coli*, or *Staphylococcus aureus* to resensitize tumours to subsequent therapies in breast cancer patients[265,266]. Allicin and glucose oxidase work in concert to increase intracellular oxidative stress and disulfide stress, which causes ferroptosis and disulfidptosis and eliminates *Pseudomonas aeruginosa*, *Enterococcus*, *E. coli*, and *Staphylococcus aureus* in breast cancer[267]. The co-delivery of lauric acid and a platinum prodrug synergistically prompts biofilm disruption against *F. nucleatum* by generating ROS through peroxidase-like activity and improves the efficacy of platinum treatment in CRC[268]. Tellurium and berberine has also been proven to have antibacterial properties[269,270].

In summary, antibiotics and biological products eliminate intratumoural pathogenic bacteria, thereby sensitizing tumours to conventional therapies. By overcoming the limitations of traditional antibiotics, bacteriophage-based therapies offer a personalized and potent approach to cancer treatment.

5.2. *Engineered bacteria*

With the unique advantages of bacteria, including rapid proliferation, precise tumour targeting ability, genetic manipulability, and genetic stability, attenuated bacteria expand rapidly, driven by physical, chemical, and synthetic biology engineering[271]. Currently, the application of engineered bacteria is mainly focused on the following fields.

5.2.1. Cancer immunotherapy

The strategic deployment of engineered bacteria to activate anti-tumour immunity represents a paradigm shift in oncology and builds on historical precedents such as the BCG and tetanus vaccines[272,273]. New approaches have leveraged engineered bacteria to function as dynamic anti-cancer immunomodulators that directly reprogram the TME and systemic immunity. Attenuation of *Salmonella typhimurium* strains, for example, is shown to enhance $CD4^+$ T-cell infiltration in a CRC model[274] and to upregulate caspase-11-driven noncanonical inflammasome signalling in a melanoma model[275]. These strains also synergize with photothermal therapy[276] or calcium carbonate-mineralized platforms to generate autologous breast cancer vaccines *in situ*[276]. *E. coli* has emerged as a versatile ally, as the intratumoural injection of *E. coli* or its outer membrane vesicles (OMVs) normalizes tumour vasculature[277,278], polarizes macrophages towards proinflammatory M1 phenotypes, and recruits cytotoxic T lymphocytes through CCL5-dependent chemotaxis in advanced-stage solid tumours[279]. Similarly, engineered *E. coli* variants—such as aptamer-conjugated strains[280] or attenuated bacteria[281]—deliver hepatitis B surface antigens to HCC[282], drive DCs maturation, and stimulate systemic helper T cell 1/cytotoxic T lymphocytes responses in bladder cancer[283]. Besides, *Lactococcus lactis* increases $CD103^+$ DCs in melanoma-draining lymph nodes[284], and *Peptostreptococcus anaerobius*-inspired biomimetic nanovaccines suppress MDSCs and M2-like macrophages to prevent CRC recurrence[285]. Notably, EVs derived from *Bacteroides fragilis* activate cGAS−STING signalling to increase DC immunogenicity in breast cancer[286].

Additionally, bacteria engineered to cancer vaccine. Flagellate bacteria act as antigens at tumour margins to prime adaptive immunity in melanoma[287]. Anaerobe-targeted therapies, such as *Cutibacterium acnes*, *Clostridium novyi-NT* spores, *Salmonella* or *Propionibacterium acnes*, exploit hypoxic niches to induce immunogenic cell death, M1 macrophage polarization, and granuloma-associated helper T cell 1 cytokine storms (*e.g.*, TNF-α, IFN-γ)[288−291]. *Staphylococcus aureus* α-haemolysin enhances the expression of PD-L1 and the infiltration of facilitated $CD8^+$ T cells in TNBC[292]. Antigen vaccines with several bacteria have been directly constructed to inhibit breast cancer metastasis and activate immunity[293]. Moreover, in breast cancer, the *F. nucleatum* membrane has been used as a vaccine adjuvant to activate immunity[294]. *Mycobacterium tuberculosis* contains pathogen-associated molecular patterns recognized by antigen-presenting cells and adhesion molecules that are shown to facilitate the invasion of antigen-presenting cells by *Mycobacterium tuberculosis* in a breast cancer model[295] (Fig. 6 and Supporting Information Table S3).

5.2.2. Engineered bacteria for drug delivery

Engineered bacteria for drug delivery are rapidly expanding for cancer therapy[195,296]. As a living drug uniquely equipped with the ability to colonize solid tumours and overcome barriers[297], this self-guided targeting of bacteria enables the precise delivery of

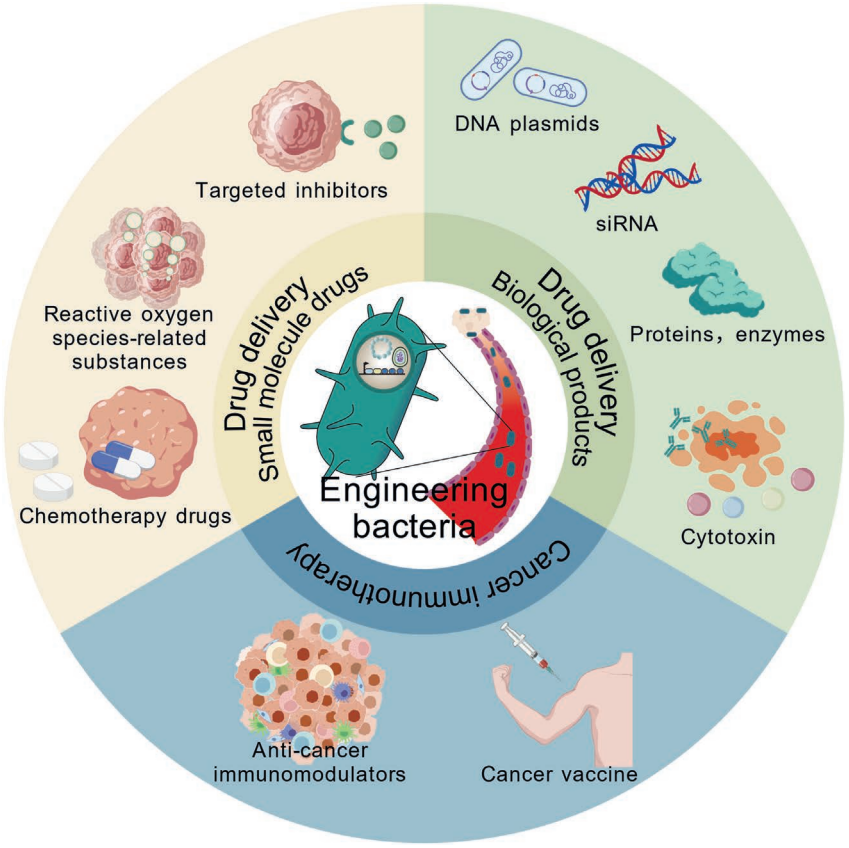

Figure 6 Bacteria used in cancer immunotherapy or act as carriers for delivery of small molecule drugs and biological products. (A) Bacterial vectors carry small-molecule drugs: chemotherapy drugs, ROS-related substances, and targeted inhibitors. (B) Engineered bacteria carry biological products: DNA plasmids, small interfering RNAs (siRNAs), proteins, enzymes, and cytotoxins. (C) Bacteria are used in cancer immunotherapy: anti-cancer immunomodulators and cancer vaccines. Created with BioGDP.com[48].

therapeutic small molecule drugs and biological products, bypassing systemic toxicity[298]. Moreover, engineered bacteria have been programmed to release therapeutic cargo in response to tumour-specific stimuli (*e.g.*, low oxygen concentration, acidic pH), synchronizing drug activation with microenvironmental cues. Bacteria can also preferentially reach necrotic or hypoxic areas of tumours. Notably, by harmonizing localized immune activation and spatiotemporally controlling drug release, bacterial vectors transcend passive delivery systems and offer a paradigm shift towards adaptive, microenvironment-responsive cancer therapy[299] (Fig. 6).

Bacteria can be engineered for the targeted delivery of small molecule anticancer drugs, including chemotherapy drugs[300], ROS-related substances[301,302], and targeted inhibitors, based on the pathogenic characteristics of the tumours[303] (Fig. 6). Radioiodine-labelled, inactivated *Salmonella* can deliver internal radiotherapy ($^{125}I/^{131}I$) to both cancer cells and TAMs in CRC[304]. Parallel approaches have exploited *E. coli* Nissle 1917 to ferry bacteria-specific radiopharmaceuticals into breast tumours[305]. Doxorubicin encapsulated in a magnetic NPs−*E. coli* conjugate has been delivered to melanoma and breast cancer cells[306,307]. Meanwhile, *Bifidobacterium longum* and *E. coli* MG1655 have been used for the targeted delivery of small molecule drugs, such as cytosine deaminase and tyrosinase, to tumours[303,308,309]. Moreover, natural anaerobic sulfate-reducing *Desulfovibrio* is constructed to dissimilate sulfate into sulfide, which amplifies oxidative stress to trigger ferroptosis and apoptosis in breast cancer cells[310].

Engineered bacteria can also be used for the delivery of biological products, including DNA plasmids, siRNAs, proteins, enzymes, cytotoxins, collagenase, or gene-editing machinery, into malignant sites. For example, engineered *S. typhimurium* secretes a fusion toxin TGF-α−PE38 (*Pseudomonas aeruginosa* exotoxin A) that selectively eradicates EGFR-overexpressing breast cancer[311,312]. *S. choleraesuis*, *E. coli* MG1655, *E coli* Nissle 1917, *and Salmonella* VNP20009 have been used to deliver endostatin DNA and cytolysin from haemolysin E DNA plasmids, L-arginine DNA, CD47 and SIRPα siRNA, respectively, to tumours[313−316]. Moreover, hypoxia-targeting *E. coli* drives therapeutic payloads such as thioredoxin-binding protein-2 into tumour cores, to induce selective tumour damage in the hypoxic niche of colon tumours[302]. Probiotic *E. coli* or *Staphylococcus epidermidis* expressing catalase catalyzed H_2O_2 decomposition into O_2, alleviating hypoxia to radiosensitize tumours[317−321]. An engineered *Lactobacillus acidophilus* is developed for the codelivery of lactate oxidase and horseradish peroxidase to disrupt lactate homeostasis in breast cancer[322]. Additionally, *Salmonella typhimurium*, *Clostridium* species, and *E. coli* strains have been reprogrammed to secrete bacterial collagenases or *Streptomyces omiyaensis* trypsin, which degrade tumour extracellular matrix components such as collagens I and IV[323−326]. Furthermore, strains such as *Brevibacillus choshinensis*, *Salmonella typhimurium* VNP20009*, Clostridium sporogenes*, *Salmonella*, and *Mycobacterium smegmatis* that have been transfected with DNA plasmids, secrete cytokines such as IFN-α/γ, IL-2, IL-10, IL-18, IL-15, and GM-CSF. This triggers systemic tumour antigen-specific responses[327−329], and amplifies T/NK cell cytolytic activity and proliferation[330−334], which reverses T-cell exhaustion and directly suppresses tumour metastasis[335−338]. Additionally, *E. coli* Nissle 1917 can express ICIs that target PD-1, PD-L1, or CTLA-4, which each disrupt immunosuppressive checkpoints. Beyond live bacteria, the role of microbial EVs in microbiota−host interactions are also important. An anti-EGFR scFV plasmid loaded in *E. coli* BL21-derived OMVs is developed for TNBC[277].

5.2.3. Engineered bacteria for cancer therapy in clinical trials Recent research highlights nearly 70 engineered bacteria-based therapies in clinical trials stage for cancer treatment, such as pancreatic cancer, lung cancer, urothelial carcinoma, gastrointestinal, pancreas, bone, and gynaecologic cancers. These clinical trials cover more than 16 bacterial species, with *L. monocytogenes* and *Salmonella enterica* the most extensively exploited[339]. Notably, among these 70 clinical trials, 58 are for cancer vaccines, four are associated with anti-cancer immunomodulators, six are related to bacteria-based drug delivery vectors, and the other two are associated with probiotics for microecological modulation (Supporting Information Table S4).

Listeria monocytogenes is one of the most common bacteria that has been studied in current clinical studies. *Listeria monocytogenes* is advantageous for cytosolic antigen processing and presentation on MHC-I, as it is specialized to enter the cytosol of infected cells, thereby activating desirable immune-sensing pathways. ADXS11−001 is a vaccine based on an attenuated live strain of the *Listeria monocytogenes*, which is administered to 290 patients with HPV associated cancers. 62.5% of the patients show a T-cell response in a phase II study (NCT02002182). Another cancer vaccine, *Clostridium novyi-NT* spores, enhances a drug response and triggers inflammatory signals in individuals with drug-resistant solid tumours, which induce tumour shrinkage in 41% of patients and stable disease in a total of 81% in a phase I study (NCT01924689). Moreover, BCG entered phase III clinical trials for bladder cancer treatment (NCT06241755, NCT06747455) with positive results in phase I/II.

Moreover, as an anti-cancer immunomodulator, EXL01 is designed based on a single strain of *F. prausnitzii*, which is expected to improve nivolumab treatment for non-small cell lung cancer patients in a phase I/II clinical trial (NCT06448572). Meanwhile, *Salmonella typhimurium* VNP20009, an L-mentholase expression-deficient mutant strain, is being constructed for patients with malignant pleural and abdominal effusions *via* intravitreal injection as part of an early-stage phase I study (NCT06178003).

Furthermore, six engineered bacteria for drug delivery of biological products, including IL-2, STING agonist, deaminase, and TLR protein, are currently in clinical trials. A phase I/II clinical trial for a combination of *Salmonella* expressing cytosine deaminase and 5-fluorocytosine shows promising results in locally transforming 5-fluorocytosine to its active form in solid tumours[303]. Subsequently, a phase I study of oral attenuated *Salmonella typhimurium* containing human IL-2 increase peripheral blood NK cell counts in patients with metastatic gastrointestinal cancers (NCT01099631). Additionally, two probiotic products, *Lactobacillus lactis* and a combination of eight probiotics (VSL#3®), have entered the clinical trial stage, which is designed to enhance the response of existing therapy (NCT06097468, NCT01579591). The phase III clinical trial of VSL#3® reported encouraging results in patients receiving concurrent pelvic radiation therapy.

Together, all these advance reveals good trends for clinical translation of engineered bacteria-based products. Nevertheless, among these 70 clinical trials based on engineered bacteria, 17 trials were terminated, one study was suspended, and two studies were withdrawn.

6. Discussion and future perspectives

The tumour microbiome is now recognized as a pivotal player in cancer biology, including driving progression, modulating therapeutic responses, and serving as a therapeutic target[340]. Tumour-associated bacteria exhibit spatiotemporal heterogeneity. For example, *F. nucleatum* and *Bacteroides* are frequently detected in the invasive margin in CRC, a region associated with increased tumour cell motility and metastatic potential. In the tumour periphery, which has increased vascularity and immune cell activity, a more diverse microbiota that includes *Lactobacillus* and *Bifidobacterium* is present; this may exert antitumour effects through metabolite production[25]. Another study showed that the intratumoural bacteria content at the OTU level in ICC tumour tissue was nearly 34% higher than that in the paracancerous tissues[94], indicating the high diversity of bacteria composition across different regions of the same tumour. Moreover, bacterial composition can vary across the various stages of tumour progression. For example, early-stage CRC is often characterized by a relative enrichment of bacteria involved in inflammation and DNA damage, such as *F. nucleatum* and *pks*$^{+}$*E. coli*. These bacteria contribute to oncogenic processes by inducing chronic inflammation and genotoxic stress. As tumours advance to later stages (TNM III−IV), the microbiota further shifts. Late-stage CRC is associated with increased abundances of *Streptococcus anginosus*, *Peptostreptococcus anaerobius*, and *Veillonella parvula*, which are linked to increased metastatic potential and poor prognosis. These heterogeneities are due to the various tumour molecular subtypes, spatial location, progression stage, genetic alterations, and the presence of multiple subclones. Still, they are also influenced by variations of angiogenesis, oxygen levels, microbial sources, endocytosis, and micropinocytosis[25,26]. Notably, Udayasuryan et al. introduced the tissue-engineered models, which could illustrate the host-microbiota interactions in cancer[341]. These models not only maintain the genetic constitution of the host but also do so in a physiologically relevant 3D structure that consists of multiple, differentiated cell types functioning in synergism as in native tissue, which helps to investigate the role of individual bacterial interactions with the host.

Intratumoural bacteria affect the entire process of tumour development. The intratumoural bacteria inhibit tumour growth by appropriating the nutrients needed for tumour proliferation, which triggers apoptosis. The apoptotic substances of the tumour serve as antigens to regulate the immune response. In contrast, intratumoural bacteria produce some substances necessary for tumour proliferation, reprogramming tumour metabolism, and tumour progression. The lactic acid secreted by intratumoural bacteria changes the TME through the Warburg effect, promoting tumour angiogenesis and drug resistance. Moreover, bacteria affect tumour cells through multiple pathways. The molecular mechanisms involving STAT3, NF-κB, Hippo, and Wnt/β-catenin pathways are dysregulated in gastric cancer caused by *H. pylori*, while *H. pylori* induces oxidative stress, DNA damage, chronic inflammation, and cell apoptosis—key cellular events that pave the way for carcinogenesis[342]. Additionally, altered nutrients and signals in the TME can lead to metabolic immune suppression of effector cells and promote regulatory immune cells[343].

Therapeutic approaches leveraging intratumoural or exogenously engineered bacteria remain a valid potential option for overcoming the limitations of conventional cancer treatments. Over the past two decades, antibiotics and biological products have been developed to eradicate the cancer-promoting bacteria. Nevertheless, traditional antibiotics may disrupt the homeostasis of the microbiome. Microbial depletion strategies—*via* antibiotics or catalytic nanomedicine—resensitize tumours to conventional therapies by dismantling bacteria-driven resistance mechanisms. The development of new antibacterial substances that specifically target a particular genus of bacteria will precisely eliminate specific bacteria within tumours while enhancing the efficacy of drugs without affecting the regulatory system of the body. Meanwhile, more engineered bacterial products should be explored to meet the unmet need for clinical cancer treatments. For example, similar to oncolytic viruses, oncolytic bacteria have the potential to be developed as an anti-cancer strategy[344]. Notably, EVs also have the potential value not only for cancer antiopathogenesis but also for cancer theranostics, which may have lots of clinical translational opportunities due to their unique attributes[345].

Currently, seven clinical trials for antibiotic-based combined therapies targeting tumour-associated bacteria, and 70 clinical trials for engineered bacteria therapies have entered the clinical trial stage for cancer treatment (Tables S2−S4). There are 58 clinical trials related to cancer vaccines, four studies for anti-cancer immune regulators, six trials related to engineered bacteria-based drug delivery vectors, and two studies for probiotics. Notably, 14 clinical trials for cancer vaccines based on *Clostridium novyi-NT* spores or *Listeria monocytogenes* by intravenous injection were terminated due to insufficient clinical efficacy, serious adverse events, or mortality. These serious adverse events may due to the bacterial attenuation process not being thorough enough. For example, LPS is not only a major virulence factor of *Clostridium novyi-NT* spores but also the primary substance that stimulates TNF secretion. *Listeria monocytogenes* has been made safer by deleting *prfA*, the master virulence regulator gene. Nevertheless, *prfA*-deficient *Listeria monocytogenes* cannot escape from the phagosome into the cytosol of the infected cells, which would prevent the tumour antigens expressed by the vaccine strains from accessing the cytosol for processing and cell surface presentation[346].

Despite the rapid development of bacterial-based technologies, several key challenges and future work should be considered. First, the mechanism of crosstalk between intratumoural microbes and the host microenvironment, as well as the origins of intratumoural bacteria, requires further investigation. This includes examining whether oral microbiota or gut microbes alter the composition of intratumoural microbes. The characteristics of the host microenvironment also need identification[1,85]. Second, the mechanism of spatiotemporal heterogeneity warrants in-depth exploration, particularly regarding the diversity of intratumoural bacteria within the same cancer. Notably, bacteria at different stages of cancer exhibit distinct functions, and the same bacteria in different cancers yield different outcomes. These aspects will help in biomarker-driven drug development in the era of personalized therapies. Moreover, the efficacy of engineered bacteria is likely to vary depending on the administration route[92,347]. Third, the safety of engineered bacteria needs to be monitored, which may induce the adverse effects associated with current immunotherapies (particularly ICIs), including systemic immune responses, hypertension, body temperature rise, and fatigue (NCT00623831). The use of attenuated bacteria systemically may bring some additional toxicity risk, such as potential symptomatic infections and off-target effects. Thus, using engineered probiotics or direct intratumoural administration may enhance safety in the future. Fourth, live bacteria exhibit several limitations, including inaccurate effective doses, poor bacterial positioning[348], accumulation

in the liver and kidneys[349], low gene transfection efficiency, and instability. For example, similar to the live cell products, live bacteria show unique dose-response relationships that differ from those of traditional drugs. The effective dose of bacteria may depend more on the individual conditions within the target tumour as well as the attribute that live bacteria proliferate in target tissues rather than the delivered dose[350]. Therefore, future efforts should focus on developing safer and highly reliable targeted bacterial carriers for drug delivery, reducing the side effects and the accumulation of bacteria in target organs, especially with regard to tumour colonization upon systemic administration. For example, locally delivered strategies, such as engineered bacterial targeting respiratory tract tumours and microneedles targeting skin tumours, may overcome some side effects[351]. Moreover, establishing a correlation between the optimal dose of bacteria and the improved pharmacokinetic parameters in the context of the specific target cancer type is essential. Furthermore, modifying the vector and gene may improve low gene transfection efficiency and gene instability. Additionally, reducing costs for future clinical applications could benefit from the high efficiency of plasmid integration in engineered bacteria. Additionally, combining multiple therapeutic modalities in a single bacterial strain with improved pharmacokinetics will enhance efficacy.

7. Methods

The methods and abbreviation list are saved in the Supporting Information

Acknowledgments

The National Natural Science Foundation of China provided funding for this study. China (Nos. 82272769 and 81972392).

Author contributions

Conceptualization, Xiaowen Jiang, Chunyan Zhang, and Simeng Cao collected the literature and drafted the manuscript. Yeheng Peng, Mingyi Zhao assisted in organizing literature for treatment and put forward valuable suggestions. Xuyao Zhang, Yuan Gao conceived and designed the study. The final draft of the work was approved by all authors.

Declaration of generative AI in scientific writing

Artificial intelligence (AI) and AI-assisted technologies were not used in writing this manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. Supporting information

Supporting information to this article can be found online at https://doi.org/10.1016/j.apsb.2026.03.022.

References

1. Cao Y, Xia H, Tan X, Shi C, Ma Y, Meng D, et al. Intratumoural microbiota: a new frontier in cancer development and therapy. *Signal Transduct Target Ther* 2024;**9**:15.
2. El Tekle G, Garrett WS. Bacteria in cancer initiation, promotion and progression. *Nat Rev Cancer* 2023;**23**:600−18.
3. Kwon SY, Thi-Thu Ngo H, Son J, Hong Y, Min JJ. Exploiting bacteria for cancer immunotherapy. *Nat Rev Clin Oncol* 2024;**21**: 569−89.
4. Xue C, Chu Q, Zheng Q, Yuan X, Su Y, Bao Z, et al. Current understanding of the intratumoral microbiome in various tumors. *Cell Rep Med* 2023;**4**:100884.
5. Jiang H, Li L, Bao Y, Cao X, Ma L. Microbiota in tumors: new factor influencing cancer development. *Cancer Gene Ther* 2024;**31**: 1773−85.
6. Abe S, Masuda A, Matsumoto T, Inoue J, Toyama H, Sakai A, et al. Impact of intratumoral microbiome on tumor immunity and prognosis in human pancreatic ductal adenocarcinoma. *J Gastroenterol* 2024;**59**:250−62.
7. Nakashima C, Yamamoto K, Kishi S, Sasaki T, Ohmori H, Fujiwara-Tani R, et al. *Clostridium perfringens* enterotoxin induces claudin-4 to activate YAP in oral squamous cell carcinomas. *Oncotarget* 2020; **11**:309−21.
8. Bender MJ, McPherson AC, Phelps CM, Pandey SP, Laughlin CR, Shapira JH, et al. Dietary tryptophan metabolite released by intratumoral *Lactobacillus reuteri* facilitates immune checkpoint inhibitor treatment. *Cell* 2023;**186**:1846−62.
9. Elkrief A, Montesion M, Sivakumar S, Hale C, Bowman AS, Begum Bektas A, et al. Intratumoral *Escherichia* is associated with improved survival to single-agent immune checkpoint inhibition in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2024;**42**: 3339−49.
10. Huang ST, Chen J, Lian LY, Cai HH, Zeng HS, Zheng M, et al. Intratumoral levels and prognostic significance of *Fusobacterium nucleatum* in cervical carcinoma. *Aging (Albany NY)* 2020;**12**: 23337−50.
11. Zheng DW, Dong X, Pan P, Chen KW, Fan JX, Cheng SX, et al. Phage-guided modulation of the gut microbiota of mouse models of colorectal cancer augments their responses to chemotherapy. *Nat Biomed Eng* 2019;**3**:717−28.
12. Xie XT, Guan M, Cheng K, Li Y, Zhang B, Zhou YT, et al. Programmable engineered bacteria as sustained-releasing antibody factory *in situ* for enhancing tumor immune checkpoint therapy. *Sci Adv* 2025;**11**:eadt7298.
13. Yang L, Li A, Wang Y, Zhang Y. Intratumoral microbiota: roles in cancer initiation, development and therapeutic efficacy. *Signal Transduct Target Ther* 2023;**8**:35.
14. Situ Y, Zhang P, Zhang C, Jiang A, Zhang N, Zhu L, et al. The metabolic dialogue between intratumoural microbes and cancer: implications for immunotherapy. *EBioMedicine* 2025;**115**:105708.
15. Gagliani N, Hu B, Huber S, Elinav E, Flavell RA. The fire within: microbes inflame tumors. *Cell* 2014;**157**:776−83.
16. Dudgeon LS, Dunkley EV. The micrococcus neoformans: its cultural characters and pathogenicity and the results of the estimation of the opsonic and agglutinative properties of the serum of patients suffering from malignant disease on this organism and on the *Staphylococcus albus*. *J Hyg (Lond)* 1907;**7**:13−21.
17. Livingston-Wheeler therapy. *CA Cancer J Clin* 1990;**40**:103−8.
18. Sepich-Poore GD, Zitvogel L, Straussman R, Hasty J, Wargo JA, Knight R. The microbiome and human cancer. *Science* 2021;**371**:1331.
19. Mukherjee N, Julian E, Torrelles JB, Svatek RS. Effects of *Mycobacterium bovis Calmette et Guérin* (BCG) in oncotherapy: bladder cancer and beyond. *Vaccine* 2021;**39**:7332−40.
20. Wotherspoon AC, Ortiz-Hidalgo C, Falzon MR, Isaacson PG. *Helicobacter pylori*-associated gastritis and primary B-cell gastric lymphoma. *Lancet* 1991;**338**:1175−6.

21. Dohlman AB, Arguijo Mendoza D, Ding S, Gao M, Dressman H, Iliev ID, et al. The cancer microbiome atlas: a pan-cancer comparative analysis to distinguish tissue-resident microbiota from contaminants. *Cell Host Microbe* 2021;**29**:281−98.
22. Battaglia TW, Mimpen IL, Traets JJH, van Hoeck A, Zeverijn LJ, Geurts BS, et al. A pan-cancer analysis of the microbiome in metastatic cancer. *Cell* 2024;**187**:2324−35.
23. Xie Y, Xie F, Zhou X, Zhang L, Yang B, Huang J, et al. Microbiota in tumors: from understanding to application. *Adv Sci (Weinh)* 2022;**9**: e2200470.
24. Xie Z, Wu Z, Liu Y, Gu Y, Niu J, Lv K. Intratumoral microbiota: implications for cancer progression and treatment. *Front Microbiol* 2025;**16**:1551515.
25. Gao Z, Jiang A, Li Z, Zhu L, Mou W, Shen W, et al. Heterogeneity of intratumoral microbiota within the tumor microenvironment and relationship to tumor development. *Med Research* 2025;**1**:32−61.
26. Ma Y, Chen T, Sun T, Dilimulati D, Xiao Y. The oncomicrobiome: new insights into microorganisms in cancer. *Microb Pathog* 2024; **197**:107091.
27. Xiao Q, Chen Wj, Wu F, Zhang Xy, Li X, Wei J, et al. Individuality and generality of intratumoral microbiome in the three most prevalent gynecological malignancies: an observational study. *Microbiol Spectr* 2024;**12**:e0100424.
28. Kneis B, Wirtz S, Weber K, Denz A, Gittler M, Geppert C, et al. Colon cancer microbiome landscaping: differences in right- and left-sided colon cancer and a tumor microbiome-ileal microbiome association. *Int J Mol Sci* 2023;**24**:3265.
29. Takenaka I, Bartelli TF, Defelicibus A, Sendoya JM, Golubicki M, Robbio J, et al. Exome and tissue-associated microbiota as predictive markers of response to neoadjuvant treatment in locally advanced rectal cancer. *Front Oncol* 2022;**12**:809441.
30. Barot SV, Sangwan N, Nair KG, Schmit SL, Xiang S, Kamath S, et al. Distinct intratumoral microbiome of young-onset and average-onset colorectal cancer. *EBioMedicine* 2024;**100**:104980.
31. Liu E, Zhang F, Xu T, Ye L, Ma SSQ, Ji ZS. Relationship between tumor microbiota transcriptional activity and gene expression in breast cancer. *BMC Cancer* 2023;**23**:252.
32. Thyagarajan S, Zhang Y, Thapa S, Allen MS, Phillips N, Chaudhary P, et al. Comparative analysis of racial differences in breast tumor microbiome. *Sci Rep* 2020;**10**:14116.
33. Wang J, Li X, Wu X, Wang Z, Zhang C, Cao G, et al. Uncovering the microbiota in renal cell carcinoma tissue using 16S rRNA gene sequencing. *J Cancer Res Clin Oncol* 2021;**147**:481−91.
34. Kovaleva OV, Podlesnaya P, Sorokin M, Mochalnikova V, Kataev V, Khlopko YA, et al. Macrophage phenotype in combination with tumor microbiome composition predicts RCC patients' survival: a pilot study. *Biomedicines* 2022;**10**:1516.
35. Kovaleva O, Podlesnaya P, Rashidova M, Samoilova D, Petrenko A, Mochalnikova V, et al. Prognostic significance of the microbiome and stromal cells phenotype in esophagus squamous cell carcinoma. *Biomedicines* 2021;**9**:743.
36. Xin HY, Zou JX, Sun RQ, Hu ZQ, Chen Z, Luo CB, et al. Characterization of tumor microbiome and associations with prognosis in intrahepatic cholangiocarcinoma. *J Gastroenterol* 2024;**59**:411−23.
37. Galeano Nino JL, Wu H, LaCourse KD, Kempchinsky AG, Baryiames A, Barber B, et al. Effect of the intratumoral microbiota on spatial and cellular heterogeneity in cancer. *Nature* 2022;**611**:810−7.
38. Li M, Bao Q, Zhang Z, Wang B, Liu Z, Wen J, et al. Exceptional response to PD-1 inhibition immunotherapy in advanced metastatic osteosarcoma with tumor site infection. *J Immunother Cancer* 2022; **10**:e004673.
39. Geller LT, Barzily-Rokni M, Danino T, Jonas OH, Shental N, Nejman D, et al. Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine. *Science* 2017;**357**:1156−60.
40. Wang Q, Zhao L, Han L, Fu G, Tuo X, Ma S, et al. The differential distribution of bacteria between cancerous and noncancerous ovarian tissues in situ. *J Ovarian Res* 2020;**13**:8.
41. Shao D, Vogtmann E, Liu A, Qin J, Chen W, Abnet CC, et al. Microbial characterization of esophageal squamous cell carcinoma and gastric cardia adenocarcinoma from a high-risk region of China. *Cancer* 2019;**125**:3993−4002.
42. Lam KC, Vyshenska D, Hu J, Rodrigues RR, Nilsen A, Zielke RA, et al. Transkingdom network reveals bacterial players associated with cervical cancer gene expression program. *PeerJ* 2018;**6**:e5590.
43. Xue C, Gu X, Shi Q, Ma X, Jia J, Su Y, et al. The interaction between intratumoral bacteria and metabolic distortion in hepatocellular carcinoma. *J Transl Med* 2024;**22**:237.
44. Mao Q, Ma W, Wang Z, Liang Y, Zhang T, Yang Y, et al. Differential flora in the microenvironment of lung tumor and paired adjacent normal tissues. *Carcinogenesis* 2020;**41**:1094−103.
45. Yu S, Ding Y, Wang X, Kin Ng S, Cao S, Liu W, et al. Intratumoral bacteria dysbiosis is associated with human papillary thyroid cancer and correlated with oncogenic signaling pathways. *Engineering* 2023;**28**:179−92.
46. Guan SW, Lin Q, Wu XD, Yu HB. Weighted gene coexpression network analysis and machine learning reveal oncogenome associated microbiome plays an important role in tumor immunity and prognosis in pan-cancer. *J Transl Med* 2023;**21**:537.
47. Zhang H, Xiong X, Cheng M, Ji L, Ning K. Deep learning enabled integration of tumor microenvironment microbial profiles and host gene expressions for interpretable survival subtyping in diverse types of cancers. *mSystems* 2024;**9**:e0139524.
48. Jiang S, Li H, Zhang L, Mu W, Zhang Y, Chen T, et al. Generic diagramming platform (GDP): a comprehensive database of high-quality biomedical graphics. *Nucleic Acids Res* 2025;**53**:D1670−6.
49. Xu H, Leng J, Liu F, Chen T, Qu J, Yang Y, et al. Tumor microbiota of renal cell carcinoma affects clinical prognosis by influencing the tumor immune microenvironment. *Heliyon* 2024;**10**:e38310.
50. Zhang Y, Lin H, Liang L, Jin S, Lv J, Zhou Y, et al. Intratumoral microbiota as a novel prognostic indicator in bladder cancer. *Sci Rep* 2024;**14**:22198.
51. Yao Z, Huang H, Zhang S, Wang S, Xia Q, Liu Z. Exploring the bladder tissue microbiome in patients with muscle-invasive bladder cancer using 2bRAD-M sequencing. *Oncologie* 2024;**26**:395−406.
52. Chen L, Xu Q, Chen W, Liu J, Xu T, Yang J, et al. Tumor-colonizing *Lachnoclostridium*-mediated chemokine expression enhances the immune infiltration of bladder urothelial carcinoma. *Cancer Immunol Immunother* 2025;**74**:62.
53. Ma J, Gnanasekar A, Lee A, Li WT, Haas M, Wang-Rodriguez J, et al. Influence of intratumor microbiome on clinical outcome and immune processes in prostate cancer. *Cancers (Basel)* 2020;**12**: 2524.
54. Guan X, Bu F, Fu Y, Zhang H, Xiang H, Chen X, et al. Immunogenic peptides putatively from intratumor microbes: opportunities for colorectal cancer treatment. *iScience* 2024;**27**:111338.
55. An HJ, Partha MA, Lee H, Lau BT, Pavlichin DS, Almeda A, et al. Tumor-associated microbiome features of metastatic colorectal cancer and clinical implications. *Front Oncol* 2023;**13**:1310054.
56. Mima K, Nishihara R, Qian ZR, Cao Y, Sukawa Y, Nowak JA, et al. *Fusobacterium nucleatum* in colorectal carcinoma tissue and patient prognosis. *Gut* 2016;**65**:1973−80.
57. Kerdreux M, Edin S, Lowenmark T, Bronnec V, Lofgren-Burstrom A, Zingmark C, et al. *Porphyromonas gingivalis* in colorectal cancer and its association to patient prognosis. *J Cancer* 2023; **14**:1479−85.
58. Hamada T, Zhang X, Mima K, Bullman S, Sukawa Y, Nowak JA, et al. *Fusobacterium nucleatum* in colorectal cancer relates to immune response differentially by tumor microsatellite instability status. *Cancer Immunol Res* 2018;**6**:1327−36.
59. Byrd DA, Fan W, Greathouse KL, Wu MC, Xie H, Wang X. The intratumor microbiome is associated with microsatellite instability. *J Natl Cancer Inst* 2023;**115**:989−93.
60. Zhang H, Liao Y, Zhang H, Wu J, Zheng D, Chen Z. Cytotoxin-associated gene A increases carcinogenicity of *Helicobacter pylori* in colorectal adenoma. *Int J Biol Markers* 2020;**35**:19−25.

61. Yu J, Liang Y, Zhang Q, Ding H, Xie M, Zhang J, et al. An interplay between human genetics and intratumoral microbiota in the progression of colorectal cancer. *Cell Host Microbe* 2025;**33**:657−70.
62. Oh HJ, Kim JH, Bae JM, Kim HJ, Cho NY, Kang GH. Prognostic impact of *Fusobacterium nucleatum* depends on combined tumor location and microsatellite instability status in stage II/III colorectal cancers treated with adjuvant chemotherapy. *J Pathol Transl Med* 2019;**53**:40−9.
63. Yang Y, Qiu YT, Li WK, Cui ZL, Teng S, Wang YD, et al. Multi-omics analysis elucidates tumor microenvironment and intratumor microbes of angiogenesis subtypes in colon cancer. *World J Gastrointest Oncol* 2024;**16**:3169−92.
64. Hilmi M, Neuzillet C, Lefevre JH, Svrcek M, Vacher S, Benhaim L, et al. Prognostic value of *Fusobacterium nucleatum* after abdominoperineal resection for anal squamous cell carcinoma. *Cancers (Basel)* 2022;**14**:1606.
65. Yang W, Zhao Y, Ge Q, Wang X, Jing Y, Zhao J, et al. Genetic mutation and tumor microbiota determine heterogenicity of tumor immune signature: evidence from gastric and colorectal synchronous cancers. *Front Immunol* 2022;**13**:947080.
66. Ai B, Mei Y, Liang D, Wang T, Cai H, Yu D. Uncovering the special microbiota associated with occurrence and progression of gastric cancer by using RNA-sequencing. *Sci Rep* 2023;**13**:5722.
67. Abate M, Vos E, Gonen M, Janjigian YY, Schattner M, Laszkowska M, et al. A novel microbiome signature in gastric cancer. *Ann Surg* 2022;**276**:605−15.
68. Wang L, Zhou J, Xin Y, Geng C, Tian Z, Yu X, et al. Bacterial overgrowth and diversification of microbiota in gastric cancer. *Eur J Gastroenterol Hepatol* 2016;**28**:261−6.
69. Peng R, Liu S, You W, Huang Y, Hu C, Gao Y, et al. Gastric microbiome alterations are associated with decreased $CD8^+$ tissue-resident memory T cells in the tumor microenvironment of gastric cancer. *Cancer Immunol Res* 2022;**10**:1224−40.
70. Yang P, Liang G, Ni Y, Chu X, Zhang X, Wang Z, et al. Investigating the role of intratumoral *Streptococcus mitis* in gastric cancer progression: insights into tumor microenvironment. *J Transl Med* 2025;**23**:126.
71. Tardy KJ, Kwak HV, Tieniber AD, Mangold AK, Perez JE, Do K, et al. Intratumoral bacteria are uncommon in gastrointestinal stromal tumor. *Ann Surg Oncol* 2025;**32**:1504−10.
72. Hsieh YY, Kuo WL, Hsu WT, Tung SY, Li C. *Fusobacterium nucleatum*-induced tumor mutation burden predicts poor survival of gastric cancer patients. *Cancers (Basel)* 2022;**15**:269.
73. Wang G, Wang H, Ji X, Wang T, Zhang Y, Jiang W, et al. Intratumoral microbiome is associated with gastric cancer prognosis and therapy efficacy. *Gut Microbes* 2024;**16**:2369336.
74. Yue K, Sheng D, Xue X, Zhao L, Zhao G, Jin C, et al. Bidirectional mediation effects between intratumoral microbiome and host DNA methylation changes contribute to stomach adenocarcinoma. *Microbiol Spectr* 2023;**11**:e0090423.
75. Kang SY, Han JH, Ahn MS, Lee HW, Jeong SH, Park JS, et al. *Helicobacter pylori* infection as an independent prognostic factor for locally advanced gastric cancer patients treated with adjuvant chemotherapy after curative resection. *Int J Cancer* 2012;**130**:948−58.
76. Xu J, Yang J, Sun Q, Chang J, Wang F. Analyses of single-cell RNA sequencing uncover the role of intratumoral *Helicobacter pylori* in shaping tumor progression and immunity in gastric cancer. *Cancer Immunol Immunother* 2025;**74**:218.
77. Zaman S, Chobrutskiy BI, Quach JU, Blanck G. Specific intratumor bacteria genera and TRG recombinations associated with greater survival probability in alimentary tract cancers. *J Gastrointest Cancer* 2023;**54**:1300−7.
78. Zhang S, Zhang S, Ma X, Zhan J, Pan C, Zhang H, et al. Intratumoral microbiome impacts immune infiltrates in tumor microenvironment and predicts prognosis in esophageal squamous cell carcinoma patients. *Front Cell Infect Microbiol* 2023;**13**:1165790.
79. Wang Y, Guo H, Gao X, Wang J. The intratumor microbiota signatures associate with subtype, tumor stage, and survival status of esophageal carcinoma. *Front Oncol* 2021;**11**:754788.
80. Yamamura K, Izumi D, Kandimalla R, Sonohara F, Baba Y, Yoshida N, et al. Intratumoral *Fusobacterium nucleatum* levels predict therapeutic response to neoadjuvant chemotherapy in esophageal squamous cell carcinoma. *Clin Cancer Res* 2019;**25**:6170−9.
81. Yamamura K, Baba Y, Nakagawa S, Mima K, Miyake K, Nakamura K, et al. Human microbiome *Fusobacterium nucleatum* in esophageal cancer tissue is associated with prognosis. *Clin Cancer Res* 2016;**22**:5574−81.
82. Wu H, Leng X, Liu Q, Mao T, Jiang T, Liu Y, et al. Intratumoral microbiota composition regulates chemoimmunotherapy response in esophageal squamous cell carcinoma. *Cancer Res* 2023;**83**:3131−44.
83. Wu H, Liu Q, Li J, Leng X, He Y, Liu Y, et al. Tumor-resident microbiota-based risk model predicts neoadjuvant therapy response of locally advanced esophageal squamous cell carcinoma patients. *Adv Sci (Weinh)* 2024;**11**:e2309742.
84. Wright RD, Bartelli TF, Baydogan S, White JR, Kim MP, Bhutani MS, et al. Bacterial and fungal characterization of pancreatic adenocarcinoma from endoscopic ultrasound-guided biopsies. *Front Immunol* 2023;**14**:1268376.
85. Riquelme E, Zhang Y, Zhang L, Montiel M, Zoltan M, Dong W, et al. Tumor microbiome diversity and composition influence pancreatic cancer outcomes. *Cell* 2019;**178**:795−806.
86. Nakano S, Kawamoto Y, Komatsu Y, Saito R, Ito K, Yamamura T, et al. Analysis of the pancreatic cancer microbiome using endoscopic ultrasound-guided fine-needle aspiration-derived samples. *Pancreas* 2022;**51**:351−7.
87. Del Castillo E, Meier R, Chung M, Koestler DC, Chen T, Paster BJ, et al. The microbiomes of pancreatic and duodenum tissue overlap and are highly subject specific but differ between pancreatic cancer and noncancer subjects. *Cancer Epidemiol Biomarkers Prev* 2019;**28**:370−83.
88. Nilsson HO, Stenram U, Ihse I, Wadstrom T. *Helicobacter* species ribosomal DNA in the pancreas, stomach and duodenum of pancreatic cancer patients. *World J Gastroenterol* 2006;**12**:3038−43.
89. Chen RH, Cao JY, Feng S, Huang HT, Lin YM, Jiang JY, et al. Integrated chromosomal instability and tumor microbiome redefined prognosis-related subtypes of pancreatic cancer. *HBPD INT* 2024;**23**:620−7.
90. Guo W, Zhang Y, Guo S, Mei Z, Liao H, Dong H, et al. Tumor microbiome contributes to an aggressive phenotype in the basal-like subtype of pancreatic cancer. *Commun Biol* 2021;**4**:1019.
91. Fan X, Alekseyenko AV, Wu J, Peters BA, Jacobs EJ, Gapstur SM, et al. Human oral microbiome and prospective risk for pancreatic cancer: a population-based nested case-control study. *Gut* 2018;**67**:120−7.
92. Mitsuhashi K, Nosho K, Sukawa Y, Matsunaga Y, Ito M, Kurihara H, et al. Association of *Fusobacterium* species in pancreatic cancer tissues with molecular features and prognosis. *Oncotarget* 2015;**6**:7209−20.
93. Adamska A, Domenichini A, Falasca M. Pancreatic ductal adenocarcinoma: current and evolving therapies. *Int J Mol Sci* 2017;**18**:1338.
94. Huang Y, Zhu N, Zheng X, Liu Y, Lu H, Yin X, et al. Intratumor microbiome analysis identifies positive association between *Megasphaera* and survival of Chinese patients with pancreatic ductal adenocarcinomas. *Front Immunol* 2022;**13**:785422.
95. Fang Y, Liu X, Ren J, Wang X, Zhou F, Huang S, et al. Integrated analysis of microbiome and metabolome reveals signatures in PDAC tumorigenesis and prognosis. *Microbiol Spectr* 2024;**12**:e0096224.
96. Guenther M, Haas M, Heinemann V, Kruger S, Westphalen CB, von Bergwelt-Baildon M, et al. Bacterial lipopolysaccharide as negative predictor of gemcitabine efficacy in advanced pancreatic cancer-translational results from the AIO-PK0104 phase 3 study. *Br J Cancer* 2020;**123**:1370−6.

97. Zhang Z, Wang T, Xu M, Zhang Z, Wang H, Xue J, et al. Deciphering the pancreatic cancer microbiome in mainland China: impact of *Exiguobacterium/Bacillus* ratio on tumor progression and prognostic significance. *Pharmacol Res* 2024;**204**:107197.
98. Leng J, Xu H, Liu X, Yang Y, Ning C, Sun L, et al. Intratumoral microbiota of pancreatic ductal adenocarcinoma impact patient prognosis by influencing tumor microenvironment. *Discov Oncol* 2024;**15**:443.
99. Banerjee S, Tian T, Wei Z, Shih N, Feldman MD, Alwine JC, et al. The ovarian cancer oncobiome. *Oncotarget* 2017;**8**:36225−45.
100. Guo Y, Xiao Y, Zhang C, Wang Y, Cao G, Tse KY, et al. The intratumoral microbiota heterogenicity is related to the prognosis and tumorigenesis of cervical cancer. *Front Cell Infect Microbiol* 2025;**15**:1574511.
101. Jiang L, Duan B, Jia P, Zhang Y, Yan X. The role of intratumor microbiomes in cervical cancer metastasis. *Cancers (Basel)* 2023;**15**:509.
102. Hermida LC, Gertz EM, Ruppin E. Predicting cancer prognosis and drug response from the tumor microbiome. *Nat Commun* 2022;**13**:2896.
103. Zhou X, Chen L, Lin W, Zheng W, Zhang H, Zhou F. Diagnostic and prognostic potential of the intra-tumoral microbiota profile in HPV-Independent endocervical adenocarcinoma. *Front Cell Infect Microbiol* 2024;**14**:1440017.
104. Liu Y, Cao L. Intratumoral *Lactobacillus iners* as a poor prognostic biomarker and potential therapeutic target for cervical cancer. *Front Cell Infect Microbiol* 2024;**14**:1469924.
105. Rustetska N, Szczepaniak M, Goryca K, Bakula-Zalewska E, Figat M, Kowalik A, et al. The intratumour microbiota and neutrophilic inflammation in squamous cell vulvar carcinoma microenvironment. *J Transl Med* 2023;**21**:285.
106. Liu S, Pan Y, Zheng C, Zheng Q, Du Y, Zheng Y, et al. Tumor-colonizing *Pseudoalteromonas elyakovii* metabolically reprograms the tumor microenvironment and promotes breast ductal carcinoma. *mBio* 2025;**16**:e0387324.
107. Li J, Zhang Y, Cai Y, Yao P, Jia Y, Wei X, et al. Multi-omics analysis elucidates the relationship between intratumor microbiome and host immune heterogeneity in breast cancer. *Microbiol Spectr* 2024;**12**:e0410423.
108. Kim D, Yu Y, Jung KS, Kim YH, Kim JJ. Tumor microenvironment can predict chemotherapy response of patients with triple-negative breast cancer receiving neoadjuvant chemotherapy. *Cancer Res Treat* 2024;**56**:162−77.
109. Chen Y, Yang L, Huang Y, Zhu T, Zhang L, Cheng M, et al. Intratumoral microbiota predicts the response to neoadjuvant chemoimmunotherapy in triple-negative breast cancer. *J Immunother Cancer* 2025;**13**:e010365.
110. Upadhyay R, Dhakal A, Wheeler C, Hoyd R, Jagjit Singh M, Karivedu V, et al. Comparative analysis of the tumor microbiome, molecular profiles, and immune cell abundances by HPV status in mucosal head and neck cancers and their impact on survival. *Cancer Biol Ther* 2024;**25**:2350249.
111. Dou Y, Ma C, Wang K, Liu S, Sun J, Tan W, et al. Dysbiotic tumor microbiota associates with head and neck squamous cell carcinoma outcomes. *Oral Oncol* 2022;**124**:105657.
112. Wang Y, Wang Y, Wang J. A comprehensive analysis of intratumor microbiome in head and neck squamous cell carcinoma. *Eur Arch Otorhinolaryngol* 2022;**279**:4127−36.
113. Qiao H, Li H, Wen X, Tan X, Yang C, Liu N. Multi-omics integration reveals the crucial role of *Fusobacterium* in the inflammatory immune microenvironment in head and neck squamous cell carcinoma. *Microbiol Spectr* 2022;**10**:e0106822.
114. Wang H, Funchain P, Bebek G, Altemus J, Zhang H, Niazi F, et al. Microbiomic differences in tumor and paired-normal tissue in head and neck squamous cell carcinomas. *Genome Med* 2017;**9**:14.
115. Hamada M, Inaba H, Nishiyama K, Yoshida S, Yura Y, Matsumoto-Nakano M, et al. Potential role of the intratumoral microbiota in prognosis of head and neck cancer. *Int J Mol Sci* 2023;**24**:15456.
116. Mao X, Huang H, Zhao L, Li F, Wang Z, Yuan X, et al. Complex of intratumoral mycobiome and bacteriome predicts the recurrence of laryngeal squamous cell carcinoma. *Appl Environ Microbiol* 2025;**91**:e0195424.
117. Azevedo MM, Pina-Vaz C, Baltazar F. Microbes and cancer: friends or faux?. *Int J Mol Sci* 2020;**21**:3115.
118. Al-Hebshi NN, Nasher AT, Maryoud MY, Homeida HE, Chen T, Idris AM, et al. Inflammatory bacteriome featuring *Fusobacterium nucleatum* and *Pseudomonas aeruginosa* identified in association with oral squamous cell carcinoma. *Sci Rep* 2017;**7**:1834.
119. Chang C, Geng F, Shi X, Li Y, Zhang X, Zhao X, et al. The prevalence rate of periodontal pathogens and its association with oral squamous cell carcinoma. *Appl Microbiol Biotechnol* 2019;**103**:1393−404.
120. Neuzillet C, Marchais M, Vacher S, Hilmi M, Schnitzler A, Meseure D, et al. Prognostic value of intratumoral *Fusobacterium nucleatum* and association with immune-related gene expression in oral squamous cell carcinoma patients. *Sci Rep* 2021;**11**:7870.
121. Arduino PG, Carbone M, Gambino A, Cabras M, Cannarsa F, Macciotta A, et al. Challenging management of gingival squamous cell carcinoma: a 10 years single-center retrospective study on Northern-Italian patients. *Med Oral Patol Oral Cir Bucal* 2021;**26**:e21−7.
122. Qiao H, Tan XR, Li H, Li JY, Chen XZ, Li YQ, et al. Association of intratumoral microbiota with prognosis in patients with nasopharyngeal carcinoma from 2 hospitals in China. *JAMA Oncol* 2022;**8**:1301−9.
123. Zhang Q, Song J, Wu H, Wang L, Zhuo G, Li H, et al. Intratumoral microbiota associates with systemic immune inflammation state in nasopharyngeal carcinoma. *Int Immunopharmacol* 2024;**141**:112984.
124. Tan XR, Qiao H, Li YQ, Jiang W, Huang SY, Gong S, et al. Tissue-resident microbiota signature in nasopharyngeal carcinoma. *Microbiome* 2025;**13**:125.
125. Zhong G, Wei W, Liao W, Wang R, Peng Y, Zhou Y, et al. Tumor microbiome in nasopharyngeal carcinoma and its association with prognosis. *Front Oncol* 2022;**12**:859721.
126. Qi H, Gao H, Li M, Sun T, Gu X, Wei L, et al. *Parvimonas micra* promotes oral squamous cell carcinoma metastasis through TmpC−CKAP4 axis. *Nat Commun* 2025;**16**:2305.
127. Qu D, Wang Y, Xia Q, Chang J, Jiang X, Zhang H. Intratumoral microbiome of human primary liver cancer. *Hepatol Commun* 2022;**6**:1741−52.
128. Chai X, Wang J, Li H, Gao C, Li S, Wei C, et al. Intratumor microbiome features reveal antitumor potentials of intrahepatic cholangiocarcinoma. *Gut Microbes* 2023;**15**:2156255.
129. Wang L, Zhao H, Wu F, Chen JL, Xu HJ, Gong WW, et al. Bile-liver phenotype: exploring the microbiota landscape in bile and intratumor of cholangiocarcinoma. *Comput Struct Biotechnol J* 2025;**27**:1173−86.
130. Tian XF, Fan XG, Zhang Y, Huang Y, Dai H, Ying RS. Procuration and identification of bacteria in paraffin-embedded liver tissues of hepatocellular carcinoma by laser-assisted microdissection technique. *Apmis* 2008;**116**:10−5.
131. Liu B, Zhou Z, Jin Y, Lu J, Feng D, Peng R, et al. Hepatic stellate cell activation and senescence induced by intrahepatic microbiota disturbances drive progression of liver cirrhosis toward hepatocellular carcinoma. *J Immunother Cancer* 2022;**10**:e003069.
132. Sun L, Ke X, Guan A, Jin B, Qu J, Wang Y, et al. Intratumoural microbiome can predict the prognosis of hepatocellular carcinoma after surgery. *Clin Transl Med* 2023;**13**:e1331.
133. Yang HS, Zhang J, Feng HX, Qi F, Kong FJ, Zhu WJ, et al. Characterizing microbial communities and their correlation with genetic mutations in early-stage lung adenocarcinoma: implications for disease progression and therapeutic targets. *Front Oncol* 2024;**14**:1498524.
134. Shi S, Chu Y, Liu H, Yu L, Sun D, Yang J, et al. Predictable regulation of survival by intratumoral microbe-immune crosstalk in patients with lung adenocarcinoma. *Microb Cell* 2024;**11**:29−40.

135. Peters BA, Pass HI, Burk RD, Xue X, Goparaju C, Sollecito CC, et al. The lung microbiome, peripheral gene expression, and recurrence-free survival after resection of stage II non-small cell lung cancer. *Genome Med* 2022;**14**:121.
136. Yu G, Gail MH, Consonni D, Carugno M, Humphrys M, Pesatori AC, et al. Characterizing human lung tissue microbiota and its relationship to epidemiological and clinical features. *Genome Biol* 2016;**17**:163.
137. Gomes S, Cavadas B, Ferreira JC, Marques PI, Monteiro C, Sucena M, et al. Profiling of lung microbiota discloses differences in adenocarcinoma and squamous cell carcinoma. *Sci Rep* 2019;**9**:12838.
138. Su Y, Li S, Sang D, Zhang Y. The characteristics of intratumoral microbial community reflect the development of lung adenocarcinoma. *Front Microbiol* 2024;**15**:1353940.
139. Zhang M, Zhang Y, Sun Y, Wang S, Liang H, Han Y. Intratumoral microbiota impacts the first-line treatment efficacy and survival in non-small cell lung cancer patients free of lung infection. *J Healthc Eng* 2022;**2022**:5466853.
140. Jungnickel C, Schmidt LH, Bittigkoffer L, Wolf L, Wolf A, Ritzmann F, et al. IL-17C mediates the recruitment of tumor-associated neutrophils and lung tumor growth. *Oncogene* 2017;**36**:4182−90.
141. Gnanasekar A, Castaneda G, Iyangar A, Magesh S, Perez D, Chakladar J, et al. The intratumor microbiome predicts prognosis across gender and subtypes in papillary thyroid carcinoma. *Comput Struct Biotechnol J* 2021;**19**:1986−97.
142. Yuan L, Yang P, Wei G, Hu X, Chen S, Lu J, et al. Tumor microbiome diversity influences papillary thyroid cancer invasion. *Commun Biol* 2022;**5**:864.
143. Karpinets TV, Mitani Y, Chang CC, Wu X, Song X, Flores II, et al. Intratumoral microbiome of adenoid cystic carcinomas and comparison with other head and neck cancers. *Sci Rep* 2024;**14**:16300.
144. Hu J, Yang Y, Feng Y, Yu Y, Song X, Jia R. Association of intratumoral microbiota with prognosis in patients with lacrimal gland tumor. *Biomedicines* 2025;**13**:960.
145. Kalaora S, Nagler A, Nejman D, Alon M, Barbolin C, Barnea E, et al. Identification of bacteria-derived HLA-bound peptides in melanoma. *Nature* 2021;**592**:138−43.
146. Nejman D, Livyatan I, Fuks G, Gavert N, Zwang Y, Geller LT, et al. The human tumor microbiome is composed of tumor type-specific intracellular bacteria. *Science* 2020;**368**:973−80.
147. Tonneau M, Nolin-Lapalme A, Kazandjian S, Auclin E, Panasci J, Benlaifaoui M, et al. *Helicobacter pylori* serology is associated with worse overall survival in patients with melanoma treated with immune checkpoint inhibitors. *Oncoimmunology* 2022;**11**:2096535.
148. Pentimalli F, Krstic-Demonacos M, Costa C, Mutti L, Bakker EY. Intratumor microbiota as a novel potential prognostic indicator in mesothelioma. *Front Immunol* 2023;**14**:1129513.
149. Li T, Zhao Z, Peng M, Zhang L, Wang C, Luo F, et al. Multi-omics analysis reveals the interplay between intratumoral bacteria and glioma. *mSystems* 2025;**10**:e0045724.
150. Tan L, Zhang D, Li Yx, Li Y, Guo T, Sun Y, et al. Identification of intratumor bacteria-associated prognostic risk score in adrenocortical carcinoma. *Microbiol Spectr* 2024;**12**:e0372723.
151. Lu YQ, Qiao H, Tan XR, Liu N. Broadening oncological boundaries: the intratumoral microbiota. *Trends Microbiol* 2024;**32**:807−22.
152. Wang N, Wu S, Huang L, Hu Y, He X, He J, et al. Intratumoral microbiome: implications for immune modulation and innovative therapeutic strategies in cancer. *J Biomed Sci* 2025;**32**:23.
153. Yuan L, Pan L, Wang Y, Zhao J, Fang L, Zhou Y, et al. Characterization of the landscape of the intratumoral microbiota reveals that *Streptococcus anginosus* increases the risk of gastric cancer initiation and progression. *Cell Discov* 2024;**10**:117.
154. Xue C, Jia J, Gu X, Zhou L, Lu J, Zheng Q, et al. Intratumoral bacteria interact with metabolites and genetic alterations in hepatocellular carcinoma. *Signal Transduct Target Ther* 2022;**7**:335.
155. Wang G, He X, Wang Q. Intratumoral bacteria are an important "accomplice" in tumor development and metastasis. *Biochim Biophys Acta Rev Cancer* 2023;**1878**:188846.
156. Guo P, Tian Z, Kong X, Yang L, Shan X, Dong B, et al. FadA promotes DNA damage and progression of *Fusobacterium nucleatum*-induced colorectal cancer through up-regulation of chk2. *J Exp Clin Cancer Res* 2020;**39**:202.
157. Pleguezuelos-Manzano C, Puschhof J, Rosendahl Huber A, van Hoeck A, Wood HM, Nomburg J, et al. Mutational signature in colorectal cancer caused by genotoxic *pks*$^{+}$ *E. coli*. *Nature* 2020;**580**:269−73.
158. Okuda S, Shimada Y, Tajima Y, Yuza K, Hirose Y, Ichikawa H, et al. Profiling of host genetic alterations and intra-tumor microbiomes in colorectal cancer. *Comput Struct Biotechnol J* 2021;**19**:3330−8.
159. Xia X, Wu WKK, Wong SH, Liu D, Kwong TNY, Nakatsu G, et al. Bacteria pathogens drive host colonic epithelial cell promoter hypermethylation of tumor suppressor genes in colorectal cancer. *Microbiome* 2020;**8**:108.
160. Yamamoto S, Kinugasa H, Hirai M, Terasawa H, Yasutomi E, Oka S, et al. Heterogeneous distribution of *Fusobacterium nucleatum* in the progression of colorectal cancer. *J Gastroenterol Hepatol* 2021;**36**:1869−76.
161. Greathouse KL, White JR, Vargas AJ, Bliskovsky VV, Beck JA, von Muhlinen N, et al. Interaction between the microbiome and TP53 in human lung cancer. *Genome Biol* 2018;**19**:123.
162. Dong H, Tan Q, Xu Y, Zhu Y, Yao Y, Wang Y, et al. Convergent alteration of lung tissue microbiota and tumor cells in lung cancer. *iScience* 2022;**25**:103638.
163. Geng F, Zhang Y, Lu Z, Zhang S, Pan Y. *Fusobacterium nucleatum* caused DNA damage and promoted cell proliferation by the Ku70/p53 pathway in oral cancer cells. *DNA Cell Biol* 2020;**39**:144−51.
164. Parida S, Wu S, Siddharth S, Wang G, Muniraj N, Nagalingam A, et al. A procarcinogenic colon microbe promotes breast tumorigenesis and metastatic progression and concomitantly activates notch and beta-catenin axes. *Cancer Discov* 2021;**11**:1138−57.
165. Goodwin AC, Destefano Shields CE, Wu S, Huso DL, Wu X, Murray-Stewart TR, et al. Polyamine catabolism contributes to enterotoxigenic *Bacteroides fragilis*-induced colon tumorigenesis. *Proc Natl Acad Sci U S A* 2011;**108**:15354−9.
166. Koi M, Okita Y, Carethers JM. *Fusobacterium nucleatum* infection in colorectal cancer: linking inflammation, DNA mismatch repair and genetic and epigenetic alterations. *J Anus Rectum Colon* 2018;**2**:37−46.
167. Li ZR, Li J, Cai W, Lai JYH, McKinnie SMK, Zhang WP, et al. Macrocyclic colibactin induces DNA double-strand breaks *via* copper-mediated oxidative cleavage. *Nat Chem* 2019;**11**:880−9.
168. Santos JC, Brianti MT, Almeida VR, Ortega MM, Fischer W, Haas R, et al. *Helicobacter pylori* infection modulates the expression of miRNAs associated with DNA mismatch repair pathway. *Mol Carcinog* 2017;**56**:1372−9.
169. Maddocks OD, Scanlon KM, Donnenberg MS. An *Escherichia coli* effector protein promotes host mutation *via* depletion of DNA mismatch repair proteins. *mBio* 2013;**4**:e00152-13.
170. Irrazabal T, Thakur BK, Kang M, Malaise Y, Streutker C, Wong EOY, et al. Limiting oxidative DNA damage reduces microbe-induced colitis-associated colorectal cancer. *Nat Commun* 2020;**11**:1802.
171. Liu D, Liu Y, Zhu W, Lu Y, Zhu J, Ma X, et al. *Helicobacter pylori*-induced aberrant demethylation and expression of *GNB4* promotes gastric carcinogenesis *via* the Hippo-YAP1 pathway. *BMC Med* 2023;**21**:134.
172. Niwa T, Tsukamoto T, Toyoda T, Mori A, Tanaka H, Maekita T, et al. Inflammatory processes triggered by *Helicobacter pylori* infection cause aberrant DNA methylation in gastric epithelial cells. *Cancer Res* 2010;**70**:1430−40.
173. He Z, Yu J, Gong J, Wu J, Zong X, Luo Z, et al. *Campylobacter jejuni*-derived cytolethal distending toxin promotes colorectal cancer metastasis. *Cell Host Microbe* 2024;**32**:2080−91.

174. Rubinstein MR, Wang X, Liu W, Hao Y, Cai G, Han YW. *Fusobacterium nucleatum* promotes colorectal carcinogenesis by modulating E-cadherin/beta-catenin signaling *via* its FadA adhesin. *Cell Host Microbe* 2013;**14**:195−206.
175. Vergara D, Simeone P, Damato M, Maffia M, Lanuti P, Trerotola M. The cancer microbiota: EMT and inflammation as shared molecular mechanisms associated with plasticity and progression. *J Oncol* 2019;**2019**:1253727.
176. Guo S, Chen J, Chen F, Zeng Q, Liu WL, Zhang G. Exosomes derived from *Fusobacterium nucleatum*-infected colorectal cancer cells facilitate tumour metastasis by selectively carrying *miR-1246/92b-3p/27a-3p* and CXCL16. *Gut* 2020;**70**:1507−19.
177. Sun M, Peng Z, Shen W, Guo X, Liao Y, Huang Y, et al. Synergism of *Fusobacterium periodonticum* and N-nitrosamines promote the formation of EMT subtypes in ESCC by modulating Wnt3a palmitoylation. *Gut Microbes* 2024;**16**:2391521.
178. Gnanasekaran J, Binder Gallimidi A, Saba E, Pandi K, Eli Berchoer L, Hermano E, et al. Intracellular *Porphyromonas gingivalis* promotes the tumorigenic behavior of pancreatic carcinoma cells. *Cancers* 2020;**12**:2331.
179. Xu L, Hu B, He J, Fu X, Liu N. Intratumor microbiome-derived butyrate promotes chemo-resistance in colorectal cancer. *Fron Pharmacol* 2024;**15**:1510851.
180. Mu W, Jia Y, Chen X, Li H, Wang Z, Cheng B. Intracellular *Porphyromonas gingivalis* promotes the proliferation of colorectal cancer cells *via* the MAPK/ERK signaling pathway. *Front Cell Infect Microbiol* 2020;**10**:584798.
181. Zhao F, An R, Ma Y, Yu S, Gao Y, Wang Y, et al. Integrated spatial multi-omics profiling of *Fusobacterium nucleatum* in breast cancer unveils its role in tumour microenvironment modulation and cancer progression. *Clin Transl Med* 2025;**15**:e70273.
182. Zhou Z, Chen J, Yao H, Hu H. *Fusobacterium* and colorectal cancer. *Front Oncol* 2018;**8**:371.
183. Keku TO, McCoy AN, Azcarate-Peril AM. *Fusobacterium spp.* and colorectal cancer: cause or consequence?. *Trends Microbiol* 2013;**21**:506−8.
184. Warren RL, Freeman DJ, Pleasance S, Watson P, Moore RA, Cochrane K, et al. Co-occurrence of anaerobic bacteria in colorectal carcinomas. *Microbiome* 2013;**1**:16.
185. Grivennikov SI, Wang K, Mucida D, Stewart CA, Schnabl B, Jauch D, et al. Adenoma-linked barrier defects and microbial products drive IL-23/IL-17−mediated tumour growth. *Nature* 2012;**491**:254−8.
186. Buchta Rosean C, Feng TY, Azar FN, Rutkowski MR. Impact of the microbiome on cancer progression and response to anti-cancer therapies. *Adv Cancer Res* 2019;**143**:255−94.
187. Chang Z, Guo X, Li X, Wang Y, Zang Z, Pei S, et al. Bacterial immunotherapy leveraging IL-10R hysteresis for both phagocytosis evasion and tumor immunity revitalization. *Cell* 2025;**188**:1842−57.
188. Gu J, Xu X, Li X, Yue L, Zhu X, Chen Q, et al. Tumor-resident microbiota contributes to colorectal cancer liver metastasis by lactylation and immune modulation. *Oncogene* 2024;**43**:2389−404.
189. Zhang Y, Zhang L, Zheng S, Li M, Xu C, Jia D, et al. *Fusobacterium nucleatum* promotes colorectal cancer cells adhesion to endothelial cells and facilitates extravasation and metastasis by inducing ALPK1/NF-kappaB/ICAM1 axis. *Gut Microbes* 2022;**14**:2038852.
190. Chung L, Thiele Orberg E, Geis AL, Chan JL, Fu K, DeStefano Shields CE, et al. *Bacteroides fragilis* toxin coordinates a pro-carcinogenic inflammatory cascade *via* targeting of colonic epithelial cells. *Cell Host Microbe* 2018;**23**:203−14.
191. Fassi Fehri L, Mak TN, Laube B, Brinkmann V, Ogilvie LA, Mollenkopf H, et al. Prevalence of *Propionibacterium acnes* in diseased prostates and its inflammatory and transforming activity on prostate epithelial cells. *Int J Med Microbiol* 2011;**301**:69−78.
192. Zhang T, Li Y, Zhai E, Zhao R, Qian Y, Huang Z, et al. Intratumoral *Fusobacterium nucleatum* recruits tumor-associated neutrophils to promote gastric cancer progression and immune evasion. *Cancer Res* 2025;**85**:1819−41.
193. Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. *Cell* 2006;**124**:783−801.
194. Li G, Sun Y, Huang Y, Lian J, Wu S, Luo D, et al. *Fusobacterium nucleatum*-derived small extracellular vesicles facilitate tumor growth and metastasis *via* TLR4 in breast cancer. *BMC Cancer* 2023;**23**:473.
195. Yu T, Guo F, Yu Y, Sun T, Ma D, Han J, et al. *Fusobacterium nucleatum* promotes chemoresistance to colorectal cancer by modulating autophagy. *Cell* 2017;**170**:548−63.
196. Kong C, Yan X, Zhu Y, Zhu H, Luo Y, Liu P, et al. *Fusobacterium nucleatum* promotes the development of colorectal cancer by activating a cytochrome P450/epoxyoctadecenoic acid axis *via* TLR4/Keap1/NRF2 signaling. *Cancer Res* 2021;**81**:4485−98.
197. Yang Y, Weng W, Peng J, Hong L, Yang L, Toiyama Y, et al. *Fusobacterium nucleatum* increases proliferation of colorectal cancer cells and tumor development in mice by activating toll-like receptor 4 signaling to nuclear factor-κB, and up-regulating expression of *MicroRNA-21*. *Gastroenterology* 2017;**152**:851−66.
198. Lee CH, Wu CL, Shiau AL. Toll-like receptor 4 mediates an antitumor host response induced by *Salmonella choleraesuis*. *Clin Cancer Res* 2008;**14**:1905−12.
199. Huang Q, Wei X, Li W, Ma Y, Chen G, Zhao L, et al. Endogenous *Propionibacterium acnes* promotes ovarian cancer progression *via* regulating Hedgehog signalling pathway. *Cancers (Basel)* 2022;**14**:5178.
200. Wu Y, Guo S, Chen F, Li Y, Huang Y, Liu W, et al. Fn-Dps, a novel virulence factor of *Fusobacterium nucleatum*, disrupts erythrocytes and promotes metastasis in colorectal cancer. *PLoS Pathog* 2023;**19**:e1011096.
201. Testerman TL, Morris J. Beyond the stomach: an updated view of *Helicobacter pylori* pathogenesis, diagnosis, and treatment. *World J Gastroenterol* 2014;**20**:12781−808.
202. Mai Z, Fu L, Su J, To KKW, Yang C, Xia C. Intra-tumoral *Sphingobacterium multivorum* promotes triple-negative breast cancer progression by suppressing tumor immunosurveillance. *Mol Cancer* 2025;**24**:6.
203. Gur C, Ibrahim Y, Isaacson B, Yamin R, Abed J, Gamliel M, et al. Binding of the Fap2 protein of *Fusobacterium nucleatum* to human inhibitory receptor TIGIT protects tumors from immune cell attack. *Immunity* 2015;**42**:344−55.
204. Udayasuryan B, Ahmad RN, Nguyen TTD, Umana A, Monet Roberts L, Sobol P, et al. *Fusobacterium nucleatum* induces proliferation and migration in pancreatic cancer cells through host autocrine and paracrine signaling. *Sci Signal* 2022;**15**:eabn4948.
205. Hayashi M, Ikenaga N, Nakata K, Luo H, Zhong P, Date S, et al. Intratumor *Fusobacterium nucleatum* promotes the progression of pancreatic cancer *via* the CXCL1−CXCR2 axis. *Cancer Sci* 2023;**114**:3666−78.
206. Mohamed AA, Al-Ramadi BK, Fernandez-Cabezudo MJ. Interplay between microbiota and gammadelta T cells: insights into immune homeostasis and neuro-immune interactions. *Int J Mol Sci* 2024;**25**:1747.
207. Javaheri A, Kruse T, Moonens K, Mejías-Luque R, Debraekeleer A, Asche CI, et al. *Helicobacter pylori* adhesin HopQ engages in a virulence-enhancing interaction with human CEACAMs. *Nat Microbiol* 2016;**2**:16189.
208. Gur C, Maalouf N, Shhadeh A, Berhani O, Singer BB, Bachrach G, et al. *Fusobacterium nucleatum* supresses anti-tumor immunity by activating CEACAM1. *OncoImmunology* 2019;**8**:e1581531.
209. Gur C, Maalouf N, Gerhard M, Singer BB, Emgård J, Temper V, et al. The *Helicobacter pylori* HopQ outermembrane protein inhibits immune cell activities. *OncoImmunology* 2019;**8**:e1553487.
210. Borowsky J, Haruki K, Lau MC, Dias Costa A, Väyrynen JP, Ugai T, et al. Association of *Fusobacterium nucleatum* with specific T-cell subsets in the colorectal carcinoma microenvironment. *Clin Cancer Res* 2021;**27**:2816−26.
211. Stone JK, von Muhlinen N, Zhang C, Robles AI, Flis AL, Vega-Valle E, et al. *Acidovorax temperans* skews neutrophil maturation

and polarizes Th17 cells to promote lung adenocarcinoma development. *Oncogenesis* 2024;**13**:13.
212. Jin C, Lagoudas GK, Zhao C, Bullman S, Bhutkar A, Hu B, et al. Commensal microbiota promote lung cancer development *via* γδ T cells. *Cell* 2019;**176**:998−1013.
213. Sun J, Tang Q, Yu S, Xie M, Zheng W, Chen G, et al. *Nucleatum* facilitates oral squamous cell carcinoma progression *via* GLUT1−driven lactate production. *EBioMedicine* 2023;**88**:104444.
214. He J, Chai X, Zhang Q, Wang Y, Wang Y, Yang X, et al. The lactate receptor HCAR1 drives the recruitment of immunosuppressive PMN−MDSCs in colorectal cancer. *Nat Immunol* 2025;**26**:391−403.
215. Lee JA, Yoo SY, Oh HJ, Jeong S, Cho NY, Kang GH, et al. Differential immune microenvironmental features of microsatellite-unstable colorectal cancers according to *Fusobacterium nucleatum* status. *Cancer Immunol Immunother* 2020;**70**:47−59.
216. Mima K, Sukawa Y, Nishihara R, Qian ZR, Yamauchi M, Inamura K, et al. *Fusobacterium nucleatum* and T cells in colorectal carcinoma. *JAMA Oncol* 2015;**1**:653−61.
217. Kostic Aleksandar D, Chun E, Robertson L, Glickman Jonathan N, Gallini Carey A, Michaud M, et al. *Fusobacterium nucleatum* potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. *Cell Host Microbe* 2013;**14**:207−15.
218. Park HE, Kim JH, Cho N-Y, Lee HS, Kang GH. Intratumoral *Fusobacterium nucleatum* abundance correlates with macrophage infiltration and CDKN2A methylation in microsatellite-unstable colorectal carcinoma. *Virchows Arch* 2017;**471**:329−36.
219. Ma Y, Chen H, Li H, Zheng M, Zuo X, Wang W, et al. Intratumor microbiome-derived butyrate promotes lung cancer metastasis. *Cell Rep Med* 2024;**5**:101488.
220. Hezaveh K, Shinde RS, Klotgen A, Halaby MJ, Lamorte S, Ciudad MT, et al. Tryptophan-derived microbial metabolites activate the aryl hydrocarbon receptor in tumor-associated macrophages to suppress anti-tumor immunity. *Immunity* 2022;**55**:324−40.
221. Panebianco C, Andriulli A, Pazienza V. Pharmacomicrobiomics: exploiting the drug-microbiota interactions in anticancer therapies. *Microbiome* 2018;**6**:92.
222. Choy ATF, Carnevale I, Coppola S, Meijer LL, Kazemier G, Zaura E, et al. The microbiome of pancreatic cancer: from molecular diagnostics to new therapeutic approaches to overcome chemoresistance caused by metabolic inactivation of gemcitabine. *Expert Rev Mol Diagn* 2018;**18**:1005−9.
223. Geller LT, Straussman R. Intratumoral bacteria may elicit chemoresistance by metabolizing anticancer agents. *Mol Cell Oncol* 2018;**5**:e1405139.
224. Sayin S, Rosener B, Li CG, Ho B, Ponomarova O, Ward DV, et al. Evolved bacterial resistance to the chemotherapy gemcitabine modulates its efficacy in co-cultured cancer cells. *Elife* 2023;**12**:e83140.
225. Qin G, Shao X, Liu X, Xu J, Wang X, Wang W, et al. A signaling molecule from intratumor bacteria promotes trastuzumab resistance in breast cancer cells. *Proc Natl Acad Sci U S A* 2025;**122**:e2421710122.
226. Benedetti F, Mongodin EF, Badger JH, Munawwar A, Cellini A, Yuan W, et al. Bacterial DnaK reduces the activity of anti-cancer drugs cisplatin and 5FU. *J Transl Med* 2024;**22**:269.
227. Guo S, Xing S, Wu Z, Chen F, Pan X, Li Q, et al. Leucine restriction ameliorates *Fusobacterium nucleatum*-driven malignant progression and radioresistance in nasopharyngeal carcinoma. *Cell Rep Med* 2024;**5**:101753.
228. Wu J, Wang H, Gao P, Ouyang S. Pyroptosis: induction and inhibition strategies for immunotherapy of diseases. *Acta Pharm Sin B* 2024;**14**:4195−227.
229. Liu Y, Wang WM, Zou LY, Li L, Feng L, Pan MZ, et al. Ubiquitin specific peptidase 5 mediates histidine-rich protein Hpn induced cell apoptosis in hepatocellular carcinoma through P14−P53 signaling. *Proteomics* 2017;**17**:1600350.
230. Yang X, Zhang Z, Shen X, Xu J, Weng Y, Wang W, et al. *Clostridium butyricum* and its metabolite butyrate promote ferroptosis susceptibility in pancreatic ductal adenocarcinoma. *Cell Oncol (Dordr)* 2023;**46**:1645−58.
231. Wang H, Rong X, Zhao G, Zhou Y, Xiao Y, Ma D, et al. The microbial metabolite trimethylamine N-oxide promotes antitumor immunity in triple-negative breast cancer. *Cell Metab* 2022;**34**:581−94.
232. Shi Y, Zheng W, Yang K, Harris KG, Ni K, Xue L, et al. Intratumoral accumulation of gut microbiota facilitates CD47-based immunotherapy *via* STING signaling. *J Exp Med* 2020;**217**:e20192282.
233. Lam KC, Araya RE, Huang A, Chen Q, Di Modica M, Rodrigues RR, et al. Microbiota triggers STING-type I IFN-dependent monocyte reprogramming of the tumor microenvironment. *Cell* 2021;**184**:5338−56.
234. Ghaddar B, Biswas A, Harris C, Omary MB, Carpizo DR, Blaser MJ, et al. Tumor microbiome links cellular programs and immunity in pancreatic cancer. *Cancer Cell* 2022;**40**:1240−53.
235. Chen F, Guo S, Li Y, Lu Y, Liu L, Chen S, et al. *Fusobacterium nucleatum*-driven CX3CR1$^+$ PD-L1$^+$ phagocytes route to tumor tissues and reshape tumor microenvironment. *Gut Microbes* 2025;**17**:2442037.
236. Wang X, Fang Y, Liang W, Wong CC, Qin H, Gao Y, et al. *Fusobacterium nucleatum* facilitates anti-PD-1 therapy in microsatellite stable colorectal cancer. *Cancer Cell* 2024;**42**:1729−46.
237. Wang X, Fang Y, Liang W, Wong CC, Qin H, Gao Y, et al. *Fusobacterium nucleatum* facilitates anti-PD-1 therapy in microsatellite stable colorectal cancer. *Cancer Cell* 2025;**43**:564−74.
238. Sivan A, Corrales L, Hubert N, Williams JB, Aquino-Michaels K, Earley ZM, et al. Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy. *Science* 2015;**350**:1084−9.
239. Ma WJ, Li ZH, Wu ZR, Liu F, Wang JK, Shi YJ, et al. PI3K−CCL2−CCR2−MDSCs axis: a potential pathway for tumor *Clostridia*-promoted CD8$^+$ T lymphocyte infiltration in bile tract cancers. *Neoplasia* 2023;**43**:100920.
240. Zheng L, Xu J, Sai B, Zhu Y, Wang L, Yin N, et al. Microbiome related cytotoxically active CD8$^+$ TIL are inversely associated with lung cancer development. *Front Oncol* 2020;**10**:531131.
241. Zhu G, Su H, Johnson CH, Khan SA, Kluger H, Lu L. Intratumour microbiome associated with the infiltration of cytotoxic CD8$^+$ T cells and patient survival in cutaneous melanoma. *Eur J Cancer* 2021;**151**:25−34.
242. Overacre-Delgoffe AE, Bumgarner HJ, Cillo AR, Burr AHP, Tometich JT, Bhattacharjee A, et al. Microbiota-specific T follicular helper cells drive tertiary lymphoid structures and anti-tumor immunity against colorectal cancer. *Immunity* 2021;**54**:2812−24.
243. Park SR, Kim DJ, Han SH, Kang MJ, Lee JY, Jeong YJ, et al. Diverse toll-like receptors mediate cytokine production by *Fusobacterium nucleatum* and *Aggregatibacter actinomycetemcomitans* in macrophages. *Infect Immun* 2014;**82**:1914−20.
244. Dhankhar R, Gupta V, Kumar S, Kapoor RK, Gulati P. Microbial enzymes for deprivation of amino acid metabolism in malignant cells: biological strategy for cancer treatment. *Appl Microbiol Biotechnol* 2020;**104**:2857−69.
245. Niu Y, Zhao X, Li Y, Ma X, Yang W, Ma J, et al. Neutrophil-mimicking nanomedicine eliminates tumor intracellular bacteria and enhances chemotherapy on liver metastasis of colorectal cancer. *Adv Sci (Weinh)* 2025;**28**:e04188.
246. Geng S, Guo P, Li X, Shi Y, Wang J, Cao M, et al. Biomimetic nanovehicle-enabled targeted depletion of intratumoral *Fusobacterium nucleatum* synergizes with PD-L1 blockade against breast cancer. *ACS Nano* 2024;**18**:8971−87.
247. Gao C, Wang X, Yang B, Yuan W, Huang W, Wu G, et al. Synergistic target of intratumoral microbiome and tumor by metronidazole-fluorouridine nanoparticles. *ACS Nano* 2023;**17**:7335−51.
248. Bernardo G, Le Noci V, Ottaviano E, De Cecco L, Camisaschi C, Guglielmetti S, et al. Reduction of *Staphylococcus epidermidis* in the mammary tumor microbiota induces antitumor immunity and decreases breast cancer aggressiveness. *Cancer Lett* 2023;**555**:216041.

249. Chen L, Shen J, Kang Z, Zhang Z, Zheng Z, Zhang L, et al. *Fusobacterium nucleatum*-mimicking nanovehicles to overcome chemoresistance for breast cancer treatment by eliminating tumor-colonizing bacteria. *Chem* 2024;**10**:1783−803.
250. Qiu Q, Lu D, Liu G, Yang X, Li J, Ren H, et al. Colistin crosslinked gemcitabine micelles to eliminate tumor drug resistance caused by intratumoral microorganisms. *Bioconjug Chem* 2022;**33**:1944−52.
251. Gao J, Tang L, Fu C, Cao Y, Liu H, Yin Y, et al. A nano-strategy for advanced triple-negative breast cancer therapy by regulating intratumoral microbiota. *Nano Lett* 2025;**25**:6134−44.
252. Wang M, Rousseau B, Qiu K, Huang G, Zhang Y, Su H, et al. Killing tumor-associated bacteria with a liposomal antibiotic generates neoantigens that induce anti-tumor immune responses. *Nat Biotechnol* 2024;**42**:1263−74.
253. Jiang H, Guo Y, Yu Z, Hu P, Shi J. Nanocatalytic bacteria disintegration reverses immunosuppression of colorectal cancer. *Natl Sci Rev* 2022;**9**:nwac169.
254. Han ZY, Fu ZJ, Wang YZ, Zhang C, Chen QW, An JX, et al. Probiotics functionalized with a gallium−polyphenol network modulate the intratumor microbiota and promote anti-tumor immune responses in pancreatic cancer. *Nat Commun* 2024;**15**:7096.
255. Song WF, Zheng D, Zeng SM, Zeng X, Zhang XZ. Targeting to tumor-harbored bacteria for precision tumor therapy. *ACS Nano* 2022;**16**:17402−13.
256. Kong F, Fang C, Zhang Y, Duan L, Du D, Xu G, et al. Abundance and metabolism disruptions of intratumoral microbiota by chemical and physical actions unfreeze tumor treatment resistance. *Adv Sci (Weinh)* 2022;**9**:e2105523.
257. Hu H, Xu Z, Liu J, Hu H, Yang H, Ma J, et al. Light-responsive hydrogel with nano-microstructures for bacteria eradication and tumor therapy. *ACS Appl Nano Mater* 2025;**8**:6242−54.
258. Wang X, Chen Q, Zhu Y, Wang K, Chang Y, Wu X, et al. Destroying pathogen-tumor symbionts synergizing with catalytic therapy of colorectal cancer by biomimetic protein-supported single-atom nanozyme. *Signal Transduct Target Ther* 2023;**8**:277.
259. Geng S, Xiang T, Shi Y, Cao M, Wang D, Wang J, et al. Locally producing antibacterial peptide to deplete intratumoral pathogen for preventing metastatic breast cancer. *Acta Pharm Sin B* 2025;**15**:1084−97.
260. Wang H, Liu Y, Bai C, Leung SSY. Translating bacteriophage-derived depolymerases into antibacterial therapeutics: challenges and prospects. *Acta Pharm Sin B* 2024;**14**:155−69.
261. Fluckiger A, Daillere R, Sassi M, Sixt BS, Liu P, Loos F, et al. Cross-reactivity between tumor MHC class I-restricted antigens and an enterococcal bacteriophage. *Science* 2020;**369**:936−42.
262. Li HR, Zhou Y, Ye BC. Tumor-targeted delivery of PD-1−displaying bacteriophages by *Escherichia coli* for adjuvant treatment of colorectal cancer. *ACS Synth Biol* 2025;**14**:407−19.
263. Chen Q, Zhu Y, Wang K, Wang X, Zhang Y, Zhou M, et al. Clearing intratumoral bacteria to augment tumor-therapeutic response by engineering antimicrobial dendritic mesoporous silica nanomedicine. *Nano Today* 2023;**52**:101994.
264. Chen L, Shen Y, Shi H, Chen Y, Yang T, Cao W, et al. Engineered bio-heterojunction for effective treatment of colorectal cancer through intratumoral bacteria scavenging and autophagy regulation. *Adv Funct Mater* 2025;**35**:2421288.
265. Xie Y, Wang J, Li L, Wang M, Sun J, Chang J, et al. A metal chelation therapy to effectively eliminate breast cancer and intratumor bacteria while suppressing tumor metastasis by copper depletion and zinc ions surge. *Angew Chem Int Ed Engl* 2025;**64**:e202417592.
266. Wu B, Yao C, Wang H, Dai H, Tian B, Li D, et al. Ellagic acid-protein nano-complex inhibits tumor growth by reducing the intratumor bacteria and inhibiting histamine production. *Biomaterials* 2025;**317**:123078.
267. Huo T, Zhu B, Shan X, Song J, Wang Z, Zhou J, et al. Allicin amplifies disulfidptosis during GOx catalyzing glucose-starvation for cancer therapy *via* simultaneous antimicrobial and antitumor intervention. *Chem Eng J* 2025;**505**:159871.
268. Li X, Niu J, Deng L, Yu Y, Zhang L, Chen Q, et al. Amphiphilic polymeric nanodrug integrated with superparamagnetic iron oxide nanoparticles for synergistic antibacterial and antitumor therapy of colorectal cancer. *Acta Biomater* 2024;**173**:432−41.
269. Hu JN, Ran SJ, Huang ZW, Liu YY, Hu HY, Zhou Y, et al. Antibacterial tellurium-containing polycarbonate drug carriers to eliminate intratumor bacteria for synergetic chemotherapy against colorectal cancer. *Acta Biomater* 2024;**185**:323−35.
270. Wang Y, Fu X, Zhu Y, Lin M, Cai R, Zhu Y, et al. An intratumor bacteria−targeted DNA nanocarrier for multifaceted tumor microenvironment intervention. *Mater Today Bio* 2024;**27**:101144.
271. Fan JX, Niu MT, Qin YT, Sun YX, Zhang XZ. Progress of engineered bacteria for tumor therapy. *Adv Drug Deliv Rev* 2022;**185**:114296.
272. Lai R, Ogunsola AF, Rakib T, Behar SM. Key advances in vaccine development for tuberculosis-success and challenges. *NPJ Vaccines* 2023;**8**:158.
273. Shrestha S, Aryal R, Yadav RS, Baidya S, Acharya S, Bhandari SS. Overuse of tetanus toxoid vaccine: a common but under-addressed issue in Nepal. *Ann Med Surg (Lond)* 2024;**86**:6276−9.
274. Al-Saafeen BH, Al-Sbiei A, Bashir G, Mohamed YA, Masad RJ, Fernandez-Cabezudo MJ, et al. Attenuated *Salmonella* potentiate PD-L1 blockade immunotherapy in a preclinical model of colorectal cancer. *Front Immunol* 2022;**13**:1017780.
275. Monaco A, Chilibroste S, Yim L, Chabalgoity JA, Moreno M. Inflammasome activation, NLRP3 engagement and macrophage recruitment to tumor microenvironment are all required for *Salmonella* antitumor effect. *Cancer Immunol Immunother* 2022;**71**:2141−50.
276. Zhuang Q, Xu J, Deng D, Chao T, Li J, Zhang R, et al. Bacteria-derived membrane vesicles to advance targeted photothermal tumor ablation. *Biomaterials* 2021;**268**:120550.
277. Rezaei Adriani R, Mousavi Gargari SL, Bakherad H, Amani J. Anti-EGFR bioengineered bacterial outer membrane vesicles as targeted immunotherapy candidate in triple-negative breast tumor murine model. *Sci Rep* 2023;**13**:16403.
278. Anker JF, Naseem AF, Mok H, Schaeffer AJ, Abdulkadir SA, Thumbikat P. Multi-faceted immunomodulatory and tissue-tropic clinical bacterial isolate potentiates prostate cancer immunotherapy. *Nat Commun* 2018;**9**:1591.
279. Zhu C, Liu C, Wu Q, Sheng T, Zhou R, Ren E, et al. Remolding the tumor microenvironment by bacteria augments adoptive T cell therapy in advanced-stage solid tumors. *Signal Transduct Target Ther* 2024;**9**:307.
280. Geng Z, Cao Z, Liu R, Liu K, Liu J, Tan W. Aptamer-assisted tumor localization of bacteria for enhanced biotherapy. *Nat Commun* 2021;**12**:6584.
281. Jin Y, Fu L. Engineer a double team of short-lived and glucose-sensing bacteria for cancer eradication. *Cell Rep Med* 2023;**4**:101043.
282. Yang M, Chen W, Gupta D, Mei C, Yang Y, Zhao B, et al. Nanoparticle/engineered bacteria based triple-strategy delivery system for enhanced hepatocellular carcinoma cancer therapy. *Int J Nanomedicine* 2024;**19**:3827−46.
283. Ren C, Li Y, Cong Z, Li Z, Xie L, Wu S. Bioengineered bacterial outer membrane vesicles encapsulated Polybia-mastoparan I fusion peptide as a promising nanoplatform for bladder cancer immunomodulatory chemotherapy. *Front Immunol* 2023;**14**:1129771.
284. Fan Y, Chen A, Zhu J, Liu R, Mei Y, Li L, et al. Engineered *Lactococcus lactis* intrapleural therapy promotes regression of malignant pleural effusion by enhancing antitumor immunity. *Cancer Lett* 2024;**588**:216777.
285. Zhuang X, Li B, Liu X, Fan T, Lan X, Wang X, et al. The colorectal cancer-specific microbiome regulation and immune response activation *via* an artificial biomimetic nanovaccine. *Chem Eng J* 2023;**461**:141982.
286. Zhang J, Wan S, Zhou H, Du J, Li Y, Zhu H, et al. Programmed nanocloak of commensal bacteria-derived nanovesicles amplify

strong immunoreactivity against tumor growth and metastatic progression. *ACS Nano* 2024;**18**:9613−26.
287. Wang W, Xu H, Ye Q, Tao F, Wheeldon I, Yuan A, et al. Systemic immune responses to irradiated tumours *via* the transport of antigens to the tumour periphery by injected *Flagellate* bacteria. *Nat Biomed Eng* 2022;**6**:44−53.
288. Chintalapati S, Iwata S, Miyahara M, Miyako E. Tumor-isolated *Cutibacterium acnes* as an effective tumor suppressive living drug. *Biomed Pharmacother* 2024;**170**:116041.
289. Bae GH, Ryu YH, Han J, Kim SH, Park CG, Park JH, et al. Multifunctional porous microspheres encapsulating oncolytic bacterial spores and their potential for cancer immunotherapy. *Biomater Sci* 2023;**11**:4652−63.
290. Tsuda K, Yamanaka K, Linan W, Miyahara Y, Akeda T, Nakanishi T, et al. Intratumoral injection of *Propionibacterium acnes* suppresses malignant melanoma by enhancing Th1 immune responses. *PLoS One* 2011;**6**:e29020.
291. Guo L, Ding J, Zhou W. Converting bacteria into autologous tumor vaccine *via* surface biomineralization of calcium carbonate for enhanced immunotherapy. *Acta Pharm Sin B* 2023;**13**: 5074−90.
292. Liu CC, Wolf M, Ortego R, Grencewicz D, Sadler T, Eng C. Characterization of immunomodulating agents from *Staphylococcus aureus* for priming immunotherapy in triple-negative breast cancers. *Sci Rep* 2024;**14**:756.
293. Kang Z, Chen L, Li P, Zheng Z, Shen J, Xiao Z, et al. A polyvalent vaccine for selectively killing tumor-associated bacteria to prevent cancer metastasis. *Sci Adv* 2025;**11**:eadt0341.
294. Yang QC, Wang YY, Wang S, Song A, Wang WD, Zhang L, et al. Engineered bacterial membrane biomimetic covalent organic framework as nano-immunopotentiator for cancer immunotherapy. *Bioact Mater* 2025;**47**:283−94.
295. Chen MH, Jiang J, Chen H, Wu RH, Xie W, Dai SZ, et al. Reinforcing cancer immunotherapy with engineered porous hollow *Mycobacterium tuberculosis* loaded with tumor neoantigens. *J Immunother Cancer* 2025;**13**:e010150.
296. Feng Z, Wang Y, Xu H, Guo Y, Xia W, Zhao C, et al. Recent advances in bacterial therapeutics based on sense and response. *Acta Pharm Sin B* 2023;**13**:1014−27.
297. Shuwen H, Yifei S, Xinyue W, Zhanbo Q, Xiang Y, Xi Y. Advances in bacteria-based drug delivery systems for anti-tumor therapy. *Clin Transl Immunology* 2024;**13**:e1518.
298. Ma X, Liang X, Li Y, Feng Q, Cheng K, Ma N, et al. Modular-designed engineered bacteria for precision tumor immunotherapy *via* spatiotemporal manipulation by magnetic field. *Nat Commun* 2023; **14**:1606.
299. Gurbatri CR, Arpaia N, Danino T. Engineering bacteria as interactive cancer therapies. *Science* 2022;**378**:858−64.
300. Pandey M, Choudhury H, Vijayagomaran PA, Lian PNP, Ning TJ, Wai NZ, et al. Recent update on bacteria as a delivery carrier in cancer therapy: from evil to allies. *Pharm Res* 2022;**39**:1115−34.
301. Zhang Y, Huang R, Jiang Y, Shen W, Pei H, Wang G, et al. The role of bacteria and its derived biomaterials in cancer radiotherapy. *Acta Pharm Sin B* 2023;**13**:4149−71.
302. Zhu D, Zhang J, Luo G, Duo Y, Tang BZ. Bright bacterium for hypoxia-tolerant photodynamic therapy against orthotopic colon tumors by an interventional method. *Adv Sci (Weinh)* 2021;**8**: e2004769.
303. Nemunaitis J, Cunningham C, Senzer N, Kuhn J, Cramm J, Litz C, et al. Pilot trial of genetically modified, attenuated *Salmonella* expressing the *E. coli* cytosine deaminase gene in refractory cancer patients. *Cancer Gene Ther* 2003;**10**:737−44.
304. Pei P, Zhang Y, Jiang Y, Shen W, Chen H, Yang S, et al. Pleiotropic immunomodulatory functions of radioactive inactivated bacterial vectors for enhanced cancer radio-immunotherapy. *ACS Nano* 2022; **16**:11325−37.
305. Siddiqui NA, Ventrola AJ, Hartman AR, Konare T, Kamble NS, Thomas SC, et al. An engineered probiotic platform for cancer epitope-independent targeted radionuclide therapy of solid tumors. *Adv Healthc Mater* 2023;**12**:e2202870.
306. Park BW, Zhuang J, Yasa O, Sitti M. Multifunctional bacteria-driven microswimmers for targeted active drug delivery. *ACS Nano* 2017; **11**:8910−23.
307. Ye Z, Zhou Y, Liang L, Zhao J, Liu W, Meng L, et al. Precision-engineered bacterial nanovectors for synergetic co-delivery to harness cellular senescence and immunomodulation for enhanced tumor eradication. *Chem Eng J* 2025;**505**:159533.
308. Sasaki T, Fujimori M, Hamaji Y, Hama Y, Ito K, Amano J, et al. Genetically engineered *Bifidobacterium longum* for tumor-targeting enzyme-prodrug therapy of autochthonous mammary tumors in rats. *Cancer Sci* 2006;**97**:649−57.
309. Wang L, Wu Q, Lyu Q, Lu D, Guo L, Zhong C, et al. Genetically designed living bacteria with melanogenesis for tumor-specific pigmentation and therapeutic intervention. *Adv Sci (Weinh)* 2024;**11**: e2402709.
310. Dong M, Yang X, Zhang W, Qiu Y, Song P, Liu H, et al. Living therapeutics of nonpathogenic bacteria as biosynthesis factory and active carriers for enhancing tumor-targeted therapy. *Nat Commun* 2025;**16**:6532.
311. Lee CH, Wu CL, Shiau AL. Endostatin gene therapy delivered by *Salmonella choleraesuis* in murine tumor models. *J Gene Med* 2004; **6**:1382−93.
312. Augustin LB, Milbauer L, Hastings SE, Leonard AS, Saltzman DA, Schottel JL. Virulence-attenuated *Salmonella* engineered to secrete immunomodulators reduce tumour growth and increase survival in an autochthonous mouse model of breast cancer. *J Drug Target* 2021;**29**: 430−8.
313. Chen QW, Zhang Y, Bao P, Zhang XZ. Sialidase-chimeric bioengineered bacteria for tumor-sialoglycan-triggered solid tumor therapy. *Nano Lett* 2024;**24**:10362−71.
314. Hu QL, Huang XY, Wang T, Lu ZT, Sun DC, Jin YX. Engineered probiotics-based biohybrid-driven tumor metabolic remodeling to boost tumor photoimmunotherapy. *ACS Appl Mater Interfaces* 2025; **17**:30516−32.
315. Wang Y, Fan Y, Zhang X, Liu J, Sun D, Li L, et al. *In situ* production and precise release of bioactive GM-CSF and siRNA by engineered bacteria for macrophage reprogramming in cancer immunotherapy. *Biomaterials* 2025;**317**:123037.
316. Sun T, Wang M, Zhang L, Gong M, Xie Q, Yang X, et al. Engineered bacterial biohybrid-mediated CD47−SIRPalpha blockade and HSP90 inhibition for enhanced immuno-photothermal therapy. *ACS Appl Mater Interfaces* 2025;**17**:29183−97.
317. Huang C, Wang FB, Liu L, Jiang W, Liu W, Ma W, et al. Hypoxic tumor radiosensitization using engineered probiotics. *Adv Healthc Mater* 2021;**10**:e2002207.
318. Ding S, Liu Z, Huang C, Zeng N, Jiang W, Li Q. Novel engineered bacterium/black phosphorus quantum dot hybrid system for hypoxic tumor targeting and efficient photodynamic therapy. *ACS Appl Mater Interfaces* 2021;**13**:10564−73.
319. Wang H, Gou R, Chen J, Wang Q, Li X, Chang J, et al. Catalase-positive *Staphylococcus epidermidis* based cryo-millineedle platform facilitates the photo-immunotherapy against colorectal cancer *via* hypoxia improvement. *J Colloid Interface Sci* 2024;**676**:506−20.
320. Wang T, Du M, Yuan Z, Guo J, Chen Z. Multi-functional nanosonosensitizer-engineered bacteria to overcome tumor hypoxia for enhanced sonodynamic therapy. *Acta Biomater* 2024;**189**: 519−31.
321. Lei L, Xu H, Li M, Du M, Chen Z. Dual-pathway tumor radiosensitization strategy based on engineered bacteria capable of targeted delivery of AuNPs and specific hypoxia alleviation. *J Nanobiotechnology* 2025;**23**:254.
322. Mao L, Xarpidin B, Shi R, Lin Y, Hu H, Wu C, et al. Natural enzyme-loaded polymeric stealth coating-armed engineered probiotics by disrupting tumor lactate homeostasis to synergistic metabolism−immuno−enzyme dynamic therapy. *Adv Sci (Weinh)* 2025;**12**:e2417172.

323. Ebelt ND, Zamloot V, Zuniga E, Passi KB, Sobocinski LJ, Young CA, et al. Collagenase-expressing *Salmonella* targets major collagens in pancreatic cancer leading to reductions in immunosuppressive subsets and tumor growth. *Cancers (Basel)* 2021;**13**:3565.
324. Li HR, Ye BC. Engineered probiotic-mediated intratumoral delivery and controlled release of bacterial collagenase for cancer therapy. *Synth Syst Biotechnol* 2025;**10**:226−36.
325. Wang Y, Liu Y, Zhu H, Wang D, Wang S, Xu X, et al. Bacteriolytic therapy with *Clostridium ghonii* for experimental solid tumors. *Biochem Biophys Res Commun* 2022;**634**:114−21.
326. Han Q, Yang F, Chen M, Zhang M, Wang L, Wang H, et al. Coating dormant collagenase-producing bacteria with metal-anesthetic networks for precision tumor therapy. *Adv Sci (Weinh)* 2024;**11**:e2407402.
327. Mukai H, Takahashi M, Watanabe Y. Potential usefulness of *Brevibacillus* for bacterial cancer therapy: intratumoral provision of tumor necrosis factor-alpha and anticancer effects. *Cancer Gene Ther* 2018; **25**:47−57.
328. Li F, Yang Z, Savage TM, Vincent RL, de Los Santos-Alexis K, Ahn A, et al. Programmable bacteria synergize with PD-1 blockade to overcome cancer cell−intrinsic immune resistance mechanisms. *Sci Immunol* 2024;**9**:eadn9879.
329. Wu L, Qiao L, Zhang S, Qiu J, Du Z, Sun Y, et al. Dual-engineered macrophage−microbe encapsulation for metastasis immunotherapy. *Adv Mater* 2024;**36**:e2406140.
330. Jeon HJ, Lim D, So E, Kim S, Jeong JH, Song M, et al. Controlling tumor progression and recurrence in mice through combined treatment with a PD-L1 inhibitor and a designer *Salmonella* strain that delivers GM-CSF. *Acta Pharm Sin B* 2024;**14**:5479−92.
331. Kubiak AM, Bailey TS, Dubois LJ, Theys J, Lambin P. Efficient secretion of murine IL-2 from an attenuated strain of *Clostridium sporogenes*, a novel delivery vehicle for cancer immunotherapy. *Front Microbiol* 2021;**12**:669488.
332. Qiao Y, Luo M, Wang Y, Qi H, Wang M, Pei Y, et al. Development of a bacteria−nanosapper for the active delivery of ZIF-8 particles containing therapeutic genes for cancer immune therapy. *Acta Pharm Sin B* 2024;**14**:5418−34.
333. Hua L, Yang Z, Li W, Zhang Q, Ren Z, Ye C, et al. A novel immunomodulator delivery platform based on bacterial biomimetic vesicles for enhanced antitumor immunity. *Adv Mater* 2021;**33**:e2103923.
334. Loeffler M, Le'Negrate G, Krajewska M, Reed JC. IL-18-producing *Salmonella* inhibit tumor growth. *Cancer Gene Ther* 2008;**15**:787−94.
335. Gurbatri CR, Lia I, Vincent R, Coker C, Castro S, Treuting PM, et al. Engineered probiotics for local tumor delivery of checkpoint blockade nanobodies. *Sci Transl Med* 2020;**12**:eaax0876.
336. Xu W, Ren D, Yu Z, Hou J, Huang F, Gan T, et al. Bacteria-mediated tumor immunotherapy *via* photothermally-programmed PD1 expression. *Nanoscale Adv* 2022;**4**:1577−86.
337. Mei Y, Zhu JM, Shao J, Li L, Liu FC, Sha XX, et al. Engineered *Mycobacterium smegmatis* expressing anti-PD-L1/IL-15 immunocytokine induces and activates specific antitumor immunity. *J Immunother Cancer* 2025;**13**:e010118.
338. Wang Q, Mei Y, Rao W, Hong S, Chen A, Yang Y, et al. The therapeutic effect of thermo-sensitive hydrogel loaded with recombinant *Mycobacterium smegmatis* expressing exogenous IL-15 in abdominal metastasis. *J Transl Med* 2025;**23**:509.
339. Ballister ER, Michels A, Vincent RL, Kreindler L, Chowdhury S, Upadhaya S, et al. The emerging landscape of engineered bacteria cancer therapies. *Nat Biotechnol* 2025;**43**:672−6.
340. Zhang S, Huang J, Jiang Z, Tong H, Ma X, Liu Y. Tumor microbiome: roles in tumor initiation, progression, and therapy. *Mol Biomed* 2025;**6**:9.
341. Udayasuryan B, Nguyen TTD, Slade DJ, Verbridge SS. Harnessing tissue engineering tools to interrogate host−microbiota crosstalk in cancer. *iScience* 2020;**23**:101878.
342. Duan Y, Xu Y, Dou Y, Xu D. *Helicobacter pylori* and gastric cancer: mechanisms and new perspectives. *J Hematol Oncol* 2025;**18**:10.
343. Arner EN, Rathmell JC. Metabolic programming and immune suppression in the tumor microenvironment. *Cancer Cell* 2023;**41**: 421−33.
344. Zhang X, Zang Z, Liang Z, Xu X, Zheng J, Liang N, et al. Nanobiohybrid oncolytic bacteria with optimized intratumoral distribution for combined sono-photodynamic/immunotherapy. *ACS Nano* 2025; **19**:6437−53.
345. Qian D, Xu P, Wang X, Du C, Zhao X, Xu J. Bacterial extracellular vesicles for gut microbiome-host communication and drug development. *Acta Pharm Sin B* 2025;**15**:1816−40.
346. Zhou S, Gravekamp C, Bermudes D, Liu K. Tumour-targeting bacteria engineered to fight cancer. *Nat Rev Cancer* 2018;**18**:727−43.
347. Gonzalez-Sanchez P, DeNicola GM. The microbiome(s) and cancer: know thy neighbor(s). *J Pathol* 2021;**254**:332−43.
348. Zhu J, Ke Y, Liu Q, Yang J, Liu F, Xu R, et al. Engineered *Lactococcus lactis* secreting Flt3L and OX40 ligand for *in situ* vaccination-based cancer immunotherapy. *Nat Commun* 2022;**13**:7466.
349. Chen Q, Bai H, Wu W, Huang G, Li Y, Wu M, et al. Bioengineering bacterial vesicle-coated polymeric nanomedicine for enhanced cancer immunotherapy and metastasis prevention. *Nano Lett* 2019;**20**: 11−21.
350. Queen J, Shaikh F, Sears CL. Understanding the mechanisms and translational implications of the microbiome for cancer therapy innovation. *Nat Cancer* 2023;**4**:1083−94.
351. Zhang W, Jiang Y, Liu L, Shen H, Huang X, Zheng W, et al. Implantable microneedles loaded with nanoparticles surface engineered *Escherichia coli* for efficient eradication of triple-negative breast cancer stem cells. *Nano Lett* 2025;**25**:2041−51.