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REVIEW

The emerging tumor microbe microenvironment: From delineation to multidisciplinary approach-based interventions

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Abstract Intratumoral microbiota has become research hotspots, and emerges as a non-negligent new component of tumor microenvironments (TME), due to its powerful influence on tumor initiation, metastasis, immunosurveillance and prognosis despite in low-biomass. The accumulations of microbes, and their related components and metabolites within tumor tissues, endow TME with additional pluralistic features which are distinct from the conventional one. Therefore, it's definitely necessary to comprehensively delineate the sophisticated landscapes of tumor microbe microenvironment, as well as their functions and related underlying mechanisms. Herein, in this review, we focused on the fields of tumor microbe microenvironment, including the heterogeneity of intratumor microbiota in different types of tumors, the controversial roles of intratumoral microbiota, the basic features of tumor microbe microenvironment (*i.e.*, pathogen-associated molecular patterns (PAMPs), typical microbial metabolites, autophagy, inflammation, multi-faceted immunomodulation and chemoresistance), as well as the multidisciplinary approach-based intervention of tumor microbiome for cancer therapy by applying wild-type or engineered live microbes, microbiota metabolites, antibiotics, synthetic biology and rationally designed biomaterials. We hope our work will provide valuable insight to deeply understand the interplay of cancer-immune-microbial, and facilitate the development of microbes-based tumor-specific treatments.

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1. Introduction

The microbiota refers to the collection of microorganisms (*e.g.*, bacteria, viruses, fungi, archaea, eubacteria and protists), which present primarily in multiple mucosal surfaces in individual body, including gastrointestinal tracts (GI), saliva, oral, genital mucosa and skin[1]. Theoretically, commensal microbiota exerts beneficial impacts on host's health, however, microbiome dysbiosis and disrupted mucosal environment could drive pathological contribution, even lead to carcinogenesis. Much attention and interests are used to focus on gut microbiota because the distal GI tact residing the most abundant population, however, the roles of microbiota in other sites are usually neglected since it faced tremendous challenges such as interference of contamination, irreproducibility of experiments, as well as limited technologies. With the improvements of analytic tools and detected techniques (*e.g.*, quantitative PCR, immunohistochemistry, 16S rRNA sequencing, genomics, fluorescence *in situ* hybridization, multi-omics technologies)[2,3], low-biomass microbial populations have been widely validated and accepted in different kinds of cancers like breast cancer, lung cancer, liver cancer and bone cancer, which are used to be considered sterile[3–5]. Most strikingly, instead of bulk tissue analysis, multi-omics (especially single-cell and spatial omics) could further facilitate the understanding of the spatial and cellular heterogeneity of intratumoral microbiota and molecular host−microbe interactions[6–8]. By applying *in situ* spatial-profiling technologies and single-cell RNA sequencing method concurrently, Galeano et al.[9] firstly reported that intratumoral microbiota were highly organized and populated micro-niches which were highly immuno-suppressive, less vascularized as well as lower Ki67 expression, rather than distribute randomly, suggesting the potential contribution of intratumoral microbiota to the heterogeneity of tumor microenvironments (TME).

Intratumor microbiota, emerging as a non-negligent new component of TME, actually a "permanent resident" rather than "short-term tenant", has become a hot and broad research topic with in-depth understanding of cancer-immune-microbial relationship[10]. The accumulations of microbes, microbes' residues (*i.e.*, microbe-derived membrane vesicles, peptides and nucleic acid) as well as microbial metabolites (*i.e.*, short-chain fatty acids, methylglyoxal, bile acids) within tumor tissues make TME possess additional features which are distinct from the previously well-identified one, herein identified as the "tumor microbe microenvironment"[11]. Tumor microbe microenvironment exerts crucial modulations on tumor initiation, progression, metastasis and immune responses[12,13]. With blowout studies carried out, the effects of intratumoral microbiota on antitumor immunity are gradually being deciphered, which could exert both anti-tumorigenic or pro-tumorigenic effects, dependent on microbiota compositions, host conditions as well as status of cancers[1,14]. More specifically, the anti-tumorigenic effects of intratumoral microbiota are embodied in enhanced antigen presentation, stimulative T and NK cell activation, effective immunosurveillance, as well as production of tumor-suppressive metabolites; on the contrary, their pro-tumorigenic effects are reflected in ROS upregulation, T cell inactivation, tumor-driving mutations and immunosuppression[15]. With in-depth understanding between tumor and microbiota interaction, the applications of microbiota are widely explored in cancer therapy, on one hand, they could be employed as prognostic or predictive tools, one the other hand, they could also be designed as vectors to delivery anti-tumor agents or genes to tumor sites, or produce cytotoxic drugs *in situ*[15]. Microbiota-based bioactive materials, such as bacterial outer membrane vesicles (OMVs), are excellent platforms for drug delivery due to microbiota-intrinsic tumor-targeting and penetration abilities, and natural immune adjuvant and enhancer since they could can induce both innate and adaptive immune responses[16,17]. Currently, several microbiota and their related preparations have been approved for clinical use[18], such as pegylated arginine deiminase(ADI-PEG 20), Bacille Calmette-Guérin (BCG), Talimogene laherparepvec (T-VEC), and L-asparaginase, indicating their great application potential.

Herein, in this review, we will focus on the fields of tumor microbe microenvironment, including the heterogeneity of intratumor microbiota in different types of tumors, the controversial roles of intratumoral microbiota, the basic features of tumor microbe microenvironment (*i.e.*, PAMPs, typical microbial metabolites, autophagy, inflammation, multi-faceted immunomodulation and chemoresistance), as well as the multidisciplinary approach-based intervention of tumor microbiome for cancer therapy, with an attempt to reveal the underlying mechanism of intratumor microbiota affecting tumorigenesis, metastasis, immunosurveillance, drug resistance and prognosis, and their potential therapeutic applications to facilitate cancer therapy.

2. Intratumoral microbiota—a new emerging component of TME

Mounting evidences have suggested the existence of intratumoral microbiota across a variety of cancer types[10]. As an intrinsic component, intratumoral microbes could greatly influence the physiological and pathological features of TME, such as metabolism, inflammation and immunity, which partially contribute to tumor heterogeneity and finally affect the outcome of cancer therapies.

2.1. The landscape and diversities of intratumoral microbiota

2.1.1. Intratumor bacteria-associated microbiota

Bacteria are single-cell microorganisms characterized by cell walls, flagellum and endospore. A comprehensive analysis containing 1526 tumors across seven cancer types (*i.e.*, breast, lung, ovary, pancreas, melanoma, bone, and brain tumors) identified that human tumor microbiome is composed of tumor type-specific intracellular bacteria[19]. And these intratumor bacteria are mostly intracellular presenting in both cancer and immune cells. Although each tumor type possesses a distinct microbiome

composition, species belonging to Firmicutes and Proteobacteria phylum took up most of the detected bacteria in all cancers. Besides that, taxa of the Actinobacteria phyla, including the Micrococcaceae and Corynebacteriaceae families, widely existed in non-gastrointestinal tumors such as breast, lung, and ovarian cancer. Among them, breast tumors present live intratumor bacteria mainly from four major genera, namely, *Staphylococcus*, *Enterococcus*, *Streptococcus*, and *Lactobacillus*[20]. At the species level, although *Fusobacterium nucleatum (F. nucleatum*) mainly enriched within colorectal tumors, it also existed in breast and pancreatic tumor. *Helicobacter pylori (H. pylori)*, as a typical cancer-associated bacteria, not only accounts for the most central risk for gastric cancer, but also residents within colorectal tumors and favors their metastasis to liver[21,22]. Intratumor bacteria are an intricate ecosystem, comprehensive resolution their composition will provide critical insight for the roles of bacteria in cancer onset and tumor progression.

2.1.2. *Intratumor non-bacterial microbiota*

Beyond bacteria, other components of microbiota such as fungi, mycoplasma, viruses and parasites also present within TME, and influence the pathogenesis of tumor tissues. Fungi closely correlate with cancer susceptibility. The fungi abundance was about 3000-fold in pancreatic ductal adenocarcinoma (PDA) compared to normal ones, and their community markedly enriched in *Malassezia* species, quite distinct from that of the gut[23]. *Malassezia* was proved to accelerate oncogenesis, ablating it could inhibit tumor growth. Besides that, Fungi has also been detected in colon, lung, prostate, gastric and skin cancers[24]. *Mycoplasma* infections are prevalently detected among various types of cancers, suggesting the strong interplay between *mycoplasmas* and malignancy[25]. For example, there was a significant *mycoplasma* accumulation in small-cell lung carcinoma tumor tissues compared to healthy controls[26]. Although *mycoplasmas* possess the malignant transformation and tumorigenicity potential, their pathological roles within TME still remain controversial and need further investigation. Virus infections also closely correlate with tumorigenesis. There are some well-defined cancer-related viruses, such as hepatitis B (HBV) and hepatitis C viruses (HCV), human papilloma viruses (HPV), human T-cell lymphotropic virus, Epstein-Barr virus, and Kaposi sarcoma herpes virus[1]. For example, HPV, especially high-risk types HPV16 and HPV18, have a causal effect on cervical cancer oncogenesis, HBV and HCV are associated with hepatocellular carcinoma cholangiocarcinoma. Moreover, it reported that bacteriophages might also get involved in cancer progress[27]. There are also presences of parasite signatures within TME, for example, *Blastocystis* is found predominantly in colorectal cancer, *Plasmodium* and intestinal nematode *Anisakis* are detected within prostate tumor samples, and *Strongyloides* has been associated with gastric cancers[24].

2.2. *Heterogeneity of intratumoral microbiota in different tumors*

The implications of intratumoral microbiota in various cancers are illustrated in Fig. 1A, including breast cancer, respiratory tumors, gastrointestinal cancer, reproductive system neoplasms and other tumors, and we will discuss each of them below. In general, their characterizations could be broadly grouped into two major categories: (i) comparison the composition of microbiome between tumor tissues (or precursor lesions) with para-carcinoma tissue (or health controls); and (ii) evaluation the association of intratumoral microbiome composition with prognostic events (*e.g.*, recurrence rates, mortality, and treatment response/resistance).

2.2.1. *Breast cancer*

Breast cancer, as the most frequent malignancies among women worldwide, exhibited tremendously biological and clinical heterogeneity[28,29]. The potential risk factors of breast cancer might include, but not limit to genetic susceptibility, lifestyle patterns, exogenous hormone intake and endogenous hormones fluctuation[2]. Besides that, breast microbiota is another risk factor, since different microbial profiles were identified within breast tissues[30]. As emerging component of breast cancer, tumor-resident microbiota possessed diverse biological functions to influence breast cancer pathogenesis from different perspectives[4,10,31].

Breast microbial profiles have been extensively studied and well delineated. Earlier studies reported that bacterium *Methylobacterium radiotolerans* and *Sphingomonas yanoikuyae* were relatively enriched in breast tumor tissue[7]. And dramatic reduction of total bacterial load and antibacterial response genes expression was observed in breast tumor tissue compared to paired normal adjacent tissue, revealing the protective role of bacteria in breast cancer[32–34]. By contrast, Urbaniak et al.[35,36] reported breast cancer tissues possessed higher abundances of *Bacillus*, Enterobacteriaceae and *Staphylococcus* with ability to cause DNA damage, while lower level of some beneficial lactic acid bacteria with anticarcinogenic properties. And they also declared similar microbial profiles between breast cancer tissues and paired normal tissue. Recently, Nejman et al.[19] implemented a comprehensive analysis of tumor microbiota across seven cancer types, it demonstrated that microbiota within breast tumors was remarkably richer and more diverse than the rest tumors. Live bacteria from Proteobacteria, Firmicutes, and Actinobacteria phyla were the main inhabitants within breast cancer tissue, which presented significantly higher bacterial load and richness than healthy controls. Similarly, Tzeng et al.[37] reported greater abundance of *Porphyromonas*, *Lacibacter*, *Ezakiella*, *Fusobacterium and Pseudomonas* within tumor tissues than healthy control, with more abundant in higher stage tumors *versus* the lower. As for the biological functions of breast intratumoral microbiota, Parhi et al.[38] demonstrated that *F. nucleatum* could accelerate tumor growth and metastatic progression through suppressing T cell accumulation. Despite these progresses, the exact roles of intratumoral bacteria during breast tumor cell dissemination, intravasation and extravasation, haven't been yet clearly established.

2.2.2. *Lung cancer*

Lungs used to be considered sterile due to they are lined by thin bacteriostatic mucus layers. However, bacterial DNA was commonly detected in lower respiratory tract, despite at a low-biomass (5−8.25 log copies/mL)[39,40]. The compositions of lung microbiota are substantially distinct from gut, oral, nasal, stool or skin[41]. Lungs present a complex and diverse bacteria community, *Fusobacterium, Veilonella, Neisseria, Prevotella*, and *Haemophilus* are the most abundant genera harbored in healthy lungs[42,43]. However, the microbial community are dramatically renewed and altered when local conditions change during lung pathologic process[44]. And the altered lung microbiota might be a mirror of illness associated with chronic inflammation and disease pathogenesis[42,45].

Lung cancer is closely associated with local inflammation, increased microbiota burden, as well as altered microbe composition[45,46]. Pro-inflammatory, enteric and potentially pathogenic

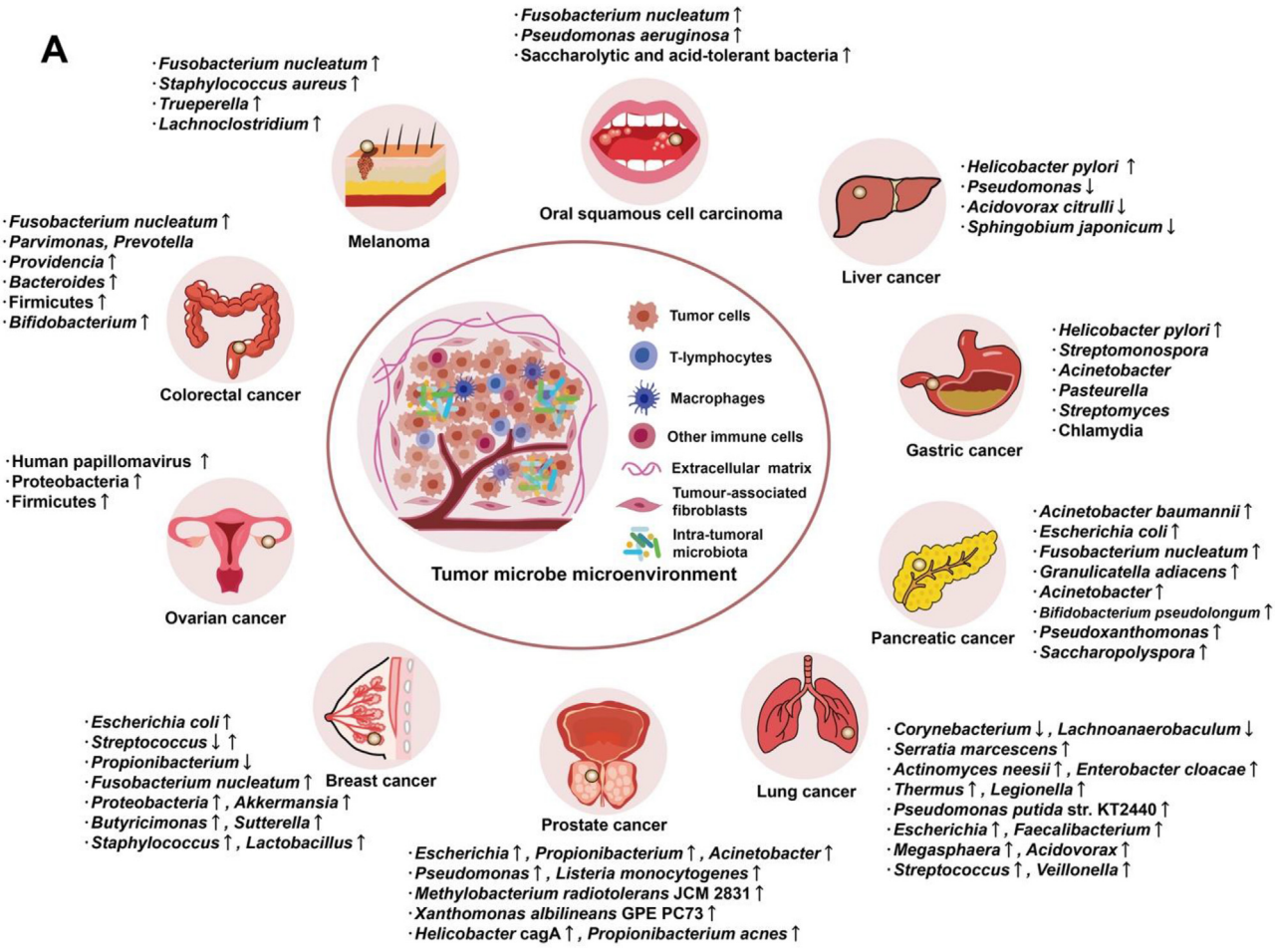

Figure 1 The characterization and implications of the intratumoral microbiota. (A) The heterogeneity of intratumoral microbiota in different tumors, including breast cancer, respiratory tumors, gastrointestinal cancer, reproductive system neoplasms and other tumors. (B) The controversial roles of intratumoral microbiota, which could be both beneficial or deleterious, dependent on their specific anti-tumorigenic or pro-tumorigenic effects *via* increasing or diminishing cancer susceptibility.

bacteria like *Brevundimonas, Faecalibacterium, Alloprevotella, Escherichia* and *Pseudomonas* were found more frequently or only presented in tumoral tissues[47−49]. Inversely, several bacterial genera were significantly decreased in lung tumor tissues compared to normal tissues, such as *Corynebacterium*, *Lachnoanaerobaculum* and *Halomonas* genera[50]. In addition, *Genusthermus* was more abundant in advanced stage cancer, *Legionella* was enriched in patients who developed metastases[41]. *Alternaria arborescens* was found as the most relevant fungus to non-small-cell lung cancer[51]. Host-microbiota interactions are critical for to establish the immune landscape of the lungs[40,52]. Using lung adenocarcinoma mouse model, it revealed that local microbiota provoked cancer-promoting inflammation by activating lung-resident δT cells, and inhibiting either microbiota or δT cells could effectively suppressed lung cancer[53,54]. In addition to pathogenic roles, lung microbiota could also exert essential effects in pulmonary immune tolerance[42]. Lung microbiota played essential roles in promoting tolerance to airway allergens in neonates, where the predominant bacterial phyla shifted Firmicutes and Gammaproteobacteria towards Bacteroidetes during the first 2 weeks after birth, which greatly contributed decreased aeroallergen responsiveness[55].

2.2.3. Gastrointestinal cancer

2.2.3.1. Pancreatic cancer. Pancreatic cancers, especially pancreatic ductal adenocarcinoma (PDAC), are highly lethal and treatment-refractory diseases with high recurrence rate after surgery[56−58]. Growing evidences suggested local pancreatic microbiota is closely related with cancer susceptibility, progression as well as therapeutic efficacy[59−61]. *H. pylori* and HBV were characterized as potential risks in pancreatic tumorigenesis[59]. *Propionibacterium acnes* (*P. acnes*) were isolated from localized pancreatic cancer tissues for the first time in 2005, which positively associated with prostatic inflammation and carcinoma evolution[62]. Moreover, Gammaproteobacteria was identified dominating taxon of intratumor microbes in human pancreatic cancer[63]. It revealed that certain pancreatic intratumoral bacteria, mainly Gammaproteobacteria, could break down gemcitabine into inactive form, targeting them with antibiotic ciprofloxacin could abrogate this chemotherapy resistance[64,65]. Owing to clinical heterogeneity, Guo et al.[66] conducted a comprehensive analysis of tumor microbiota among different PDAC subtypes, it showed that a highly aggressive tumor subtype termed 'basal-like' presented distinctive microbial communities, with enriched abundance of *Acinetobacter*, *Pseudomonas* and *Sphingopyxis* and were highly associated with carcinogenesis. As an opportunistic pathogenic bacterium, the enrichment of *Pseudomonas* was also observed in short-term survival PDAC patients[67,68]. However, intratumoral bacteria may not always be harmful in PDAC, some bacteria played protective roles and associated with improved clinical outcomes. For example, it claimed that long-term survival PDAC patients displayed higher tumor microbial diversity compared to short-term ones, and the presence and abundance of a beneficial intratumoral microbiota signature including *Pseudoxanthomonas*, *Streptomyces*, *Saccharopolyspora* and *Bacillus clausii* could be adopted to highly predict long-term survivorship[68]. Collectively, these studies highlighted the significance of intratumoral microbiota in altering the natural history of PDAC.

2.2.3.2. Colorectal cancer. Colorectal cancer (CRC) has caused huge global health burden since it once ranked third leading cause of cancer-related deaths[69]. Harboring trillions of bacteria (about 3×10^{13}), the colorectum is closely connected with gut microbiota, which greatly influence the progression and treatment response of CRC[70]. Studies have revealed microbial compositional and ecological changes in CRC patients. For example, Dejea et al.[71] have identified patchy bacterial biofilms mainly composed of *Escherichia coli* and enterotoxigenic *Bacteroides fragilis* (*B. fragilis)* in colonic mucosa of patients with familial adenomatous polyposis, suggesting the close link between colon early neoplasia and tumorigenic bacteria, consisted with several other studies[72,73]. There were some other well-documented CRC-associated taxa, such as *Fusobacterium*, *Parvimonas*, *Bacteroides* and *Prevotella*[74]. Among them, *F. nucleatum* is one of the most prevalent bacterial species in colorectal carcinogenesis[75,76]. As core member of the human oral microbiota, *F. nucleatum* could reach and localize CRC through Fap2-mediated bind to Gal-GalNAc[77]. Bullman et al.[78] found *F. nucleatum* and its associated microbiota including *Bacteroides*, *Selenomonas* and *Prevotella* species were maintained in both primary CRC and paired distant metastases, antibiotic metronidazole treatment could effectively reduce *Fusobacterium* load and overall tumor growth. Using *in situ* spatial-profiling technologies, Galeano et al.[9] further revealed host-bacterial spatial, cellular and molecular interactions of CRC. It demonstrated that *Fusobacterium* and *Bacteroides* were the most dominant genera within colorectal TME, which were inclined to populate micro-niches that were less vascularized and highly immuno-suppressive, indicating that distribution of the microbiota within TME was not random and highly organized.

2.2.3.3. Gastric cancer. Gastric cancer (GC) is the fifth most prevalent cancer globally, characterized with low early diagnosis rate and undesirable prognosis. There were intimate associations existing between gastric microbial dysbiosis and GC progress[79]. *H. pylori* is considered to be a class I carcinogen by the WHO, and the greatest risk factors for GC development, however, only about 3% of *H. pylori* infected person develop GC[80]. Several bacteria could be regularly detected in gastric biopsies associated with GC, such as the members of Proteobacteria, Firmicutes, Actinobacteria and Fusobacteria phyla, implying their potential roles on GC tumorigenesis[81−83]. Coker et al.[84] identified five GC-enriched bacterial taxa including *Peptostreptococcus stomatis*, *Streptococcus anginosus*, *(Parvimonas micra*, *Slackia exigua* and *Dialister pneumosintes*, which could be adopted as biomarkers to distinguish GC from superficial gastritis. Studies also suggested significantly different microbial compositions among gastritis, gastric adenoma, early and advanced GC[85,86]. The microbial diversity continuously decreased in its sequential process of gastric carcinogenesis, where *Lactobacillus* and *Veillonella* were enriched in GC while *Akkermansia* and *Lachnospiraceae NK4A136* were enriched in gastritis[87]. As GC is characterized with microbial dysbiosis potentially favoring carcinogenesis, the insights on gastric microbiota composition and function could provide helpful clinical implications.

2.2.4. Reproductive system neoplasms

2.2.4.1. Ovarian cancer. Ovarian cancer is one of the most lethal gynecological malignancies, both ovarian surface epithelial and fallopian tube are identified as sources of high-grade serous ovarian cancers, where the tumor carcinogenesis might attribute to these following factors, including hormonal fluctuations, pelvic inflammatory disease, and tumor local immune microenvironment[88,89].

According to several comprehensive studies, local microbial dysbiosis might play potential roles in manipulating the initiation or progression of ovarian cancer. The clinical relevance of *Chlamydia trachomatis (C. trachomatis)*, *Neisseria gonorrhoeae* and *Mycoplasma genitalium* infection with ovarian cancer susceptibility and progression has been confirmed, where *C. trachomatis* infection could increase the overall risk for ovarian cancer by 1.344-fold through causing continuous inflammation and chromosomal aberrations[90–92]. The upper reproductive tract was charactered as non-sterile tissue with unique microbiota composition in ovarian cancer patients[93,94]. Apart from the precise association with cervical cancer, HPV infection also potentially corelated with ovarian carcinogenesis, since high-risk HPV including types 16, 18 and 45 showed elevated level in malignant tissues than normal adjacent tissues, reflecting the pathogenic role of HPV in ovarian tumor[95,96]. Local Gram-negative bacteria colonization may facilitate carcinogenesis initiation and continuation, as well as metastasis formation in ovarian cancer[92]. Compared to normal distal fallopian tube tissues, decreased bacterial diversity and richness was found in ovarian cancer tissues[97]. Proteobacteria and Firmicutes were identified as the specific and key bacterial phyla associated with ovarian cancer, as well as *Lactobacillales* and *Burkholderiales* at the related taxa, *Roseomonas mucosa* and *Sphingomonas US_602* at species[19,97].

2.2.4.2. Prostate cancer. Prostate cancer possesses high morbidity and mortality rates, but the etiology and pathogenesis of this disease are still not fully understood[98–100]. Microbiota infection and infection-induced chronic inflammation has been deemed as causative factors or cofactors of prostate carcinogenesis, since epidemiological studies revealed that up to 87% prostate cancer patients contained microbial DNA in their prostates, indicating the potential pathophysiological roles of local microbiota[101–103]. Accordingly, to date, 100 species from more than 50 genera are thought to reside in the human urogenital tract. *Streptococcus,* Bacteroidetes*, Faecalibacterium, Lactobaccili,* and *Actinetobacter* were found to be more abundant in urine samples of prostate cancer patients compared to controls. The pathological prostate is non-sterile, whole-genome sequencing on prostatic tissue samples confirmed that the most abundant genera in prostate tumor microbiome (*i.e.*, *Propionibacterium, Escherichia* and *Pseudomonas*), among them, *P. acnes* was the most prevalent and collective microorganism in prostatic tissue[62,104]. As an anaerobic gram-positive skin commensal bacillus, different subtype of *P. acnes* might contribute differently to health and disease, where subtype I predominantly associated with acne while type II mainly acted as contributing agent for prostatic inflammation and cancer initiation[105–107]. *C. trachomatis* also correlated with increased risk of prostate cancer development due to its pro-inflammatory responses[108]. Additionally, *Staphylococcus* was found more frequent in the tumor than nontumor tissues[109]. Banerjee et al.[24] detected three distinct prostate cancer-specific microbiota signatures including bacterial, viral, fungal and parasitic in prostate cancer samples, which highly correlated with clinical cancer diagnostic data, and possessed great diagnostic and prognostic values. For example, parasite signatures including *Toxoplasma*, *Plasmodium*, *Schistosoma* and *Blastocystis* were detected in prostate tumor samples, which might potentially facilitate oncogenesis through inducing chromosomal damage and producing reactive ROS. Dissimilarly, Feng et al.[110] reported no significantly differential bacterial species were detected between prostate cancer specimens and their matched benign tissues, although *Escherichia*, *Propionibacterium*, *Acinetobacter* and *Pseudomonas* were characterized as the most abundant prostate microbiota, indicating they might comprise the normal prostate flora. However, they pointed out that *Pseudomonas* infection might impede metastasis based on the correlated expression between *Pseudomonas* genes and human small RNA genes. The contradictory and discrepancy among different researches might partially been explained by relatively low and dynamically changing levels of viruses and microorganisms in the prostate.

2.2.5. Other tumors

2.2.5.1. Melanoma. Human skin is a large, heterogeneous organ sustaining thriving populations of diverse microbes. Earlier research has characterized the topographical and temporal diversity of skin microbiota in healthy human, it demonstrated that *Propionibacteria* and *Staphylococci* predominated in sebaceous sites, *Corynebacteria* predominated in moist sites, *β-Proteobacteria* and *Flavobacteriales* showed greater prevalence in dry sites, suggesting the skin microbial community were greatly dependent on the specific characteristics of the skin site[111]. The bacterial biomass of melanoma is relatively lower compared to other tumor types like lung, ovarian, pancreatic or breast cancers, and the main bacteria genera identified within melanoma were *Acinetobacter*, *Actinomyces*, *Corynebacterium*, *Enterobacter* and *Streptococcus*[19,112]. It demonstrated that intratumoral bacteria could directly modulate antitumor immune responses through peptide presentation in infected melanoma cells, where bacteria-derived peptide fragments might be in complex with MHC molecules, indicating that bacterial antigens could serve as targets for immunotherapy[112,113]. Another study demonstrated that fecal microbiota transplant could overcome resistance to anti-PD-1 therapy in melanoma patients[114]. Additionally, Zhu et al.[115] reported that intratumour bacteria genus, including *Lachnoclostridium*, *Gelidibacter* and *Flammeovirga*, positively correlated with $CD8^+$ T cells infiltration and chemokine levels, and consequently influenced patient melanoma survival. Moreover, Nakatsuji et al.[116] showed that a commensal strain of 6-*N*-hydroxyaminopurine-producing *Staphylococcus epidermidis (S. epidermidis)* could suppress the growth of B16F10 melanoma as well as reduce ultraviolet-induced tumor incidence, suggesting the novel role of skin commensal bacteria in host defense and against skin cancer.

2.2.5.2. Liver cancer. Hepatocellular carcinoma (HCC) is one of the most fatal tumors due to high incidence, poor outcomes and postsurgical recurrence[117]. Chronic HBV infection and excessive alcohol consumption have been well-established as two major risk factors of HCC[118]. Chakladar et al.[119] have classified the effects of HBV and alcohol on intratumor liver microbiota due to their potential modulation of HCC pathogenesis and progression, it demonstrated that most liver microbiota were likely oncogenic and tumor-promoting after alcohol or HBV exposure. As for the intratumoral microbial community of HCC, Qu et al.[120] reported that Proteobacteria, Actinobacteria, Bacteroidetes and Firmicutes were the four dominant bacterial phyla in both liver tumor tissues and the matched adjacent tissues, while the abundance of Pseudomonadaceae was significantly decreased in tumor tissues and linearly associated with prognosis of liver cancer patients, suggesting its potential anti-tumor effects. Although many studies suggested the impacts of intratumoral microbiota on other type of

cancers, currently there were still limited reports about the community of intratumoral microbiota in liver cancer.

2.2.5.3. Bone tumor. Bone tumors, especially osteosarcoma, usually occur in young teenagers. Due to the high postoperative recurrence and metastasis rate, bone tumor therapy is challenging in clinic[121]. Although there were no direct connections between external environment within bone tumors, bacterial DNA was also detected. Nejman et al.[19] were the first to characterize intracellular bacteria within bone tumors, it demonstrated that Actinobacteria, Bacteroidetes, Fusobacteria, Cyanobacteria, Firmicutes and Proteobacteria accounted for most of the detected bacteria. Hydroxyproline, mainly derived from bone collagen, is significantly elevated in bone tumors, however, it showed that there was a specific enrichment of bacteria (*i.e.*, *MetaCyc PWY-5159*) with ability to degrade hydroxyproline in bone tumors, suggesting metabolic functions exerted by intratumor bacteria were also associated with clinical features[19,122].

In all, we have discussed the heterogeneity of intratumoral microbiota in different tumors, and there was a brief conclusive description summarized in Table 1[9,20,24,32,35,37,38,41,47,49–51,62,66,68,75–77,84,86,87,97,107,109,110,112,113,119,120,123–151].

2.3. The controversial roles of intratumoral microbiota: protective or pro-tumorigenic

The relationship between microbiota and cancer is incredibly complex, there is an intricate network among microbial infections, microbial disorders, tumorigenesis and TME. Can microbiota be the cause or the consequence of cancer development? Current available data is insufficient to draw any final conclusion. Although around 3.7×10^{30} microbes live on earth and implicate in around 20% of human malignancies, only 12 microbes (1 bacterium, 8 viruses, and 3 parasites, shown in Table 2) are recognized as human carcinogens by the International Agency for Cancer Research (IACR)[12,152]. In fact, not all microbes are pathogenic, some microbes have pro-tumorigenic effects and maintain the status of our health. Microbes could be both beneficial or deleterious, dependent on their specific anti-tumorigenic or pro-tumorigenic effects (Fig. 1B).

As for the protective role of the microbiota against tumorigenesis, the distinct mechanisms might include but not limit to the following[153]: (i) beneficial microbes compete with pathogenic ones, some beneficial bacteria such as *Clostridium* and *Lactobacillus* could initiate and form the niche, which is favorable for themselves growth but suppressive for pathogenic bacteria overgrowth[154,155]. (ii) Effective cancer immunosurveillance due to tonic stimulation and maturation of immune system, classical Coley experiments where bacterial infections resulted in established tumors regression lay the foundation of this opinion[156]. Antibiotic-treated mice showed the defective antitumor response and were more susceptible to melanoma, suggesting the importance of commensal bacteria in host immune surveillance[157]. Microbes could stimulate activation of immune cells, for example, Lactobacilla could enhance antitumor immune responses by boosting DCs, T cells, NK cells and NK T cells[158]. Recently, it demonstrated that peptides derived from intracellular bacteria could be presented by both antigen-presenting cells and tumor cells to elicit a tumor-infiltrating T cell immune response, further uncovering a potential mechanism how bacteria can influence immune system activation[112]. (iii) Producing tumor suppressive metabolites, for example, short chain fatty acids (SCFAs) produced by commensal bacteria could effectively inhibit myeloid cell-driven pro-tumorigenic inflammation as well as inflammatory cytokines secretion[159], moreover, other metabolites including biotin, cobalamin, folate, niacin, pantothenate, pyridoxine also possess anti-tumor properties[160]. (iv) Facilitating and boosting various forms of cancer therapies. Microbiota play essential roles in facilitating sensitivity to both chemotherapies and immunotherapies. Antibiotic-treated tumor-bearing mice responded poorly to oxaliplatin or immunomodulatory agent cyclophosphamide[161]. Moreover, anti-PD-1 or anti-CTLA4 efficacy also positively correlated with overall microbiota diversity[162,163].

On the other hand, the pro-tumorigenic effects of microbiota are highly convinced, as the above-mentioned carcinogenic microbes such as HBV, HCV, HPV and *H. pylori* have directly correlated with tumor initiation and progression[21]. Besides that, there are many other pathogenic organisms. And the pro-tumorigenic roles of microbiota in tumorigenesis could attribute to the following mechanisms[1,152,164]: (i) facilitating pro-carcinogenic inflammatory responses. Most of time, proinflammatory responses are pro-carcinogenic and tumor-permissive. Numerous cancer-associated microbes and their metabolites could effectively trigger and reinforce chronic cancer-associated inflammation, such as colon cancer-associated *F. nucleatum*[165]. Intratumoral or barrier-seeding microbes could activate both innate and adaptive immune system to stimulate pro-inflammatory cytokines secretion, and the cytokine-mediated signaling pathways including IL-23/IL-17 axis, TNF-α, IL-6/STAT3 axis all contribute to tumor progression and growth[152,166]. (ii) Eliciting immune-dampening responses, the prime example is HIV infection, which greatly increase the susceptibility and risk of many cancers due to systemic immunosuppression. Bacteria can also cause immunosuppressive TME by boosting Treg and MDSCs stimulation[5]. For example, *F. nucleatum* could directly inhibit NK cell cytotoxicity and T cell activation by engaging TIGIT receptors expressed on NK cells and T cells with its own Fap2 protein, thus resulting in impaired antitumor immunity[133]. (iii) Inducing genotoxic effects *via* tumor-driving mutations. Microbiota and their related metabolites could elicit DNA damage and drive somatic mutations though producing or releasing genotoxic compounds, and these processes have been directly implicated tumorigenesis. *Staphylococcus* strains could result in the accumulation of mutations in malignant T cells by secreting toxic hemolysins and enterotoxins, and *Salmonella* could directly increase oncogenic β-catenin expression by produces a protein toxin virulence factor A[167]. (iv) Regulating metabolic effects on carcinogenic compounds, it showed that microbiota secreted metabolites such as reactivated estrogens, secondary bile acids and amino acid metabolites, are important modulators to promote tumorigenesis, which work by activating pro-carcinogenic compounds, regulating hormone metabolism and modifying inflammatory pathways[13,168]. Bacteria-driven deoxycholic acid (DCA) could promote colorectal cancer development by modulating muscarinic and Wnt receptors pathways[153].

3. The basic features of tumor microbe microenvironment

The dialogues between microbe and TME are sophisticated and pluralistic, involving both cell-microbe direct coactions and messenger molecule-mediated interactions. The basic features of tumor microbe microenvironment claimed by existed studies

Table 1 A brief conclusive description of the intratumoral microbiota in various cancers.

Tumor type	Sample material and size (tumor/control)	Microorganism	Status	Function	Role	Ref.
Liver cancer	Formalin fixed paraffin embedded (FFPE)samples, 28/28 (self)	*Pseudomonas*	Decreased	Linearly associated with prognosis	Deleterious	120
	Raw whole-transcriptome RNA-sequencing data, 373/50	*A. citrulli, S. japonicum*	Decreased	Inversely associated with patient death	Protective	119
	liver specimens, 20/16	*H. pylori*	Enriched	Probably linked to the carcinogenic process	Deleterious	123
Breast cancer (BC)	Fresh human breast tissue, 58/23	*E. coli, S. epidermidis*	Enriched	Induced DNA double-stranded breaks	Deleterious	35
	Fresh human breast tissue, 10/36	*Butyricimonas, Sutterella, Akkermansia*	Enriched	N/a	N/A	124
	MMTV-PyMT spontaneous murine breast tissue, 102/18	*Staphylococcus, Lactobacillus*	Enriched	Reduced metastasis and promote circulating tumor cells survival	Deleterious	20
	Fresh-frozen human breast tissues, 221/69	*Streptococcus, Propionibacterium*	Decreased	Negatively associated with oncogenic immune features	Favorable	37
	human breast cancer tissue, 50/50	*F. nucleatum*	Enriched	Accelerated cancer progression and metastatic development	Deleterious	38
	RNA sequencing data from TCGA, 668/72	Proteobacteria	Increased	N/A	N/A	126
	FFPE and fresh-frozen breast tissues, 20/20(self)	*Methylobacterium, Sphingomonas*	Dysbiosis	Implicated in diagnosis	N/A	32
	frozen human breast tissue samples, 10/10(self)	*Streptococcus*	Enriched	N/A	N/A	126
Lung cancer	publicly available 16S rRNA gene sequence data, 356/493	*Corynebacterium, Lachnoanaerobaculum, Halomonas*	Decreased	An association between microbiome dysbiosis and cancer	N/A	50
	Human NSCLC tissue, 28/28	*A. arborescens*	Enriched	Associated with NSCLC progress	Deleterious	51
	Human NSCLC tissue, 47/0	*S. marcescens, E. cloacae, H. parainfluenzae*	Enriched	Predicted two-year survival	Deleterious	49
	Human NSCLC tissue, 47/0	*S. haemolyticus, Streptococcus*	Dysbiosis	Against lung cancer development and progression	Protective	49
	Fresh frozen human lung tumor tissue, 31/31(self)	*Thermus, Legionella*	Increased	Implied advanced stage cancer or metastases	Deleterious	41
	TCGA mRNA sequencing, 497/497	*E. coli* W3110	Dysbiosis	Correlated with survival and genomic alterations	Deleterious	127
	TCGA mRNA sequencing data, 433/433(self)	*P. putida* KT2440	Enriched	Uniquely associated with young male patients	Deleterious	127
	Human NSCLC tissue, 29/29(self)	*Pseudomonas, Faecalibacterium*	Increased	Only recurrently present in tumoral tissues	Pathogenic	47
	Bronchoalveolar fluid, 20/8	*Veillonella, Megasphaera*	Increased	Serve as biomarkers to predict lung cancer	Deleterious	128
	Lower airway brushings, 83/83(self)	*V. parvula*	Dysbiosis	Led to decreased survival and increased tumor burden	Deleterious	129
	Flash frozen human lung tumor tissue, 121/121(self)	*Acidovorax*	Enriched	Related to smoking-associated cancer patients	Deleterious	130
	Lower airway brushings, 39/46	*Streptococcus, Veillonella*	Enriched	Associated with up-regulation of PI3K pathways	Deleterious	131

(*continued on next page*)

Table 1 (*continued*)

Tumor type	Sample material and size (tumor/control)	Microorganism	Status	Function	Role	Ref.
Colorectal cancer (CRC)	FFPE human adenocarcinoma samples, 18/10	*F. nucleatum*	Enriched	Promotes colonic tumor formation	Deleterious	77
	Flash-frozen human tumor, 44/44(self)	*Fusobacterium,* Providencia	Elevated	Significantly correlated with CRC	Pathogenic	132
	Fresh colorectal carcinoma samples, 99/99(self)	*F. nucleatum*	Enriched	More likely to have regional lymph node metastases	Deleterious	75
	Human CRC tumour specimens, 11/0	*Fusobacterium, Bacteroides*	Most dominant	Induce neutrophil swarming and the migration of cancer epithelial cells	Deleterious	9
	N/A	*F. nucleatum*	N/A	Protected tumors from immune cell attack	Deleterious	133
	Human CRC tumour tissue, 95/95(self)	*Fusobacterium*	Enriched	N/A	N/A	76
	Human CRC tumour tissue, 95/95(self)	*Bacteroidetes, Firmicutes*	Depleted	N/A	N/A	76
	Human CRC tumour tissue, 50/50(self)	*Bifidobacterium*	Dysbiosis	No significant associations with mortality	N/A	134
	Tissue biopsies from patients, 36/36(self)	*Fusobacterium, Bacteroides, Parvimonas, Prevotella*	Highly varied	Correlated with colorectal carcinogenesis	N/A	135
Gastric cancer	Gastric cancer tissue, 160/160(self)	*H. pylori*	Enriched	The primary cause of gastric cancer	Deleterious	136
	Raw RNA-Seq data from NCBI, 379/348	*Helicobacter, Streptomonospora, Acinetobacter, Pasteurella, Streptomyces, Chlamydia*	Dysbiosis	Involved in tumor progression as potential characteristic genera	Deleterious	86
	Gastric biopsy tissues, 39/168	*S. anginosus, P. micra,S. exigua,*	Enriched	Form a strong co-occurrence network with disease progression.	Deleterious	84
	Gastric juice samples, 56/32	*Lactobacillus, Veillonella*	Enriched	N/A	Deleterious	87
	Biopsy specimens after surgery, 36/36	*Firmicutes, Bacteroidetes,* Proteobacteria	Enriched	N/A	Deleterious	137
Melanoma	Melanoma samples derived from patients, 9/0	*F. nucleatum, S. aureus, S. capitis;*	Enriched	Produced bacterial peptides and elicited immune reactivity	Deleterious	112,113
	Melanoma-bearing Libechov minipig, 13/13	*Fusobacterium, Trueperella*	Enriched	Indicated skin microbiome changes	N/A	138
	RNA-Seq raw data from TCGA, 447/0	*Lachnoclostridium*	Enriched	Reduced the mortality risk	Protective	115
Ovarian cancer	FFPE) human ovarian carcinoma tissues, 100/100(self)	HPV 16, 18 and 45	Enriched	Highly associated with the advanced stages of tumor	Deleterious	139
	Fresh ovarian cancer tissues, 25/25	Proteobacteria, Firmicutes	Increased	Associated with cancer development	Deleterious	97
Prostate cancer	Radical prostatectomy specimens, 65/65	*Escherichia, Propionibacterium, Acinetobacter, Pseudomonas*	Enriched	Pseudomonas infection may impede metastasis	N/A	110

	RNA-sequencing data from TCGA, 242/52	*L. monocytogenes, Methylobacterium, X. albilineans* GPE PC73;	Overrepresented	Played anti-tumor roles	Protective	140
	FFPE prostate cancer tissues, 50/15	*Helicobacter cagA*	Enriched	N/A	N/a	24
	radical prostatectomy-specimens, 16/16	*Propionibacterium*	Abundant	Suggested a possible pathophysiological correlation	N/a	109
	Prostate swabs, 71/20	*P. acnes*	Enriched	Contributing to tumor initiation or progression	Deleterious	107
	Radical prostatectomy specimens, 34/0	*P. acnes*	Enriched	Linked to the evolution of carcinoma	Deleterious	62
Pancreatic cancer	RNA-sequencing data from TCGA, 187/0	*A. ebreus, A. baumannii, G. kaustophilus, E. coli*	Enriched	Inked to metastasis and immune suppression	Deleterious	141
	Paired cyst fluid and plasma, 105/105	*F. nucleatum, G. adiacens*	Enriched	In synergy with neoplastic grade	N/A	142
	Surgical specimens, 62/0	*Acinetobacter, Pseudomonas, Sphingopyxis*	Enriched	Induce pathogen-related inflammation	Deleterious	66
	Pancreatic cyst fluids, 69/0	*Bacteroides, Escherichia, Acidaminococcus*	Enriched	Revealed specific bacterial ecosystem	N/A	143
	Pancreatic tissue specimens, 27/27(self)	Enterobacteriaceae	Dysbiosis	Might contribute to chemoresistance	N/A	144
	Murine pancreatic neoplasia, (5/5)	*B. pseudolongum*	Enriched	Promoted oncogenesis	Deleterious	145
	Surgically resected PDAC tumor, 68/0	*Pseudoxanthomonas, Saccharopolyspora, Streptomyces*	Enriched	Predicted long-term survivorship	N/A	68
Oral squamous cell carcinoma (OSCC)	Human tumor tissue, 151/0	*F. nucleatum*	Dysbiosis	Associated with a favorable prognosis	Protective	146
	Fresh OSCC biopsies, 20/20	*F. nucleatum, P. aeruginosa*	Enriched	Inflammatory bacteriome	N/A	147
	Fresh OSCC biopsies, 20/12	Saccharolytic and acid-tolerant bacteria	Enriched	N/A	N/A	148
	Resected OSCC tissue, 120/0	*F. nucleatum*	N/A	Confers chemoresistance	Deleterious	149
Esophageal cancer	N/A	*Campylobacter*	Enriched	Caused chronic esophageal inflammation	Deleterious	150
	Biopsy specimens after surgery, 67/67(self)	*Fusobacterium*	Enriched	N/A	Deleterious	137
	FFPE esophageal cancer specimens, 325/325(self)	*F. nucleatum*	Enriched	Associated with shorter survival	Deleterious	151

N/A: not applicable.

A. arborescens: *Alternaria arborescens*; *A. baumannii*: *Acinetobacter baumannii*; *A. citrulli*: *Acidovorax citrulli*; *A. ebreus*: *Acidovorax ebreus*; *B. pseudolongum*: *Bifidobacterium pseudolongum*; *E. cloacae*: *Enterobacter cloacae*; *E. coli*: *Escherichia coli*; *F. nucleatum*: *Fusobacterium nucleatum*; *G. adiacens*: *Granulicatella adiacens*; *G. kaustophilus*: *Geobacillus kaustophilus*; *H. parainfluenzae*: *Haemophilus parainfluenzae*; *H. pylori*: *Helicobacter pyloxri*; *Human papillomavirus (HPV)*; *L. monocytogenes*: *Listeria monocytogenes*; *P. acnes*: *Propionibacterium acnes*; *P. aeruginosa*: *Pseudomonas aeruginosa*; *P. micra*: *Parvimonas micra*; *P. putida*: *Pseudomonas putida*; *S. aureus*: *Staphylococcus aureus*; *S. capitis*: *Staphylococcus capitis*; *S. exigua*: *Slackia exigua*; *S. epidermidis*: *Staphylococcus epidermidis*; *S. haemolyticus*: *Staphylococcus haemolyticus*; *S. japonicum*: *Sphingobium japonicum*; *S. marcescens*: *Serratia marcescens*; *V. parvula*: *Veillonella parvula*; *X. albilineans*: *Xanthomonas albilineans*.

Table 2 Twelve carcinogenic microbes recognized by the International Agency for Cancer Research (IACR).

Infectious carcinogen		Major associated cancer
Bacteria	*H. pylori*	Gastric carcinoma (stomach cancer), mucosa-associated lymphoid tissue lymphoma
Viruses	Human papillomavirus (HPV) (high-risk types, eg, HPV16 and HPV18)	Cervical carcinoma, other anogenital cancers, oropharyngeal and other head-and-neck carcinomas
	Hepatitis B virus (HBV)	Hepatocellular carcinoma (liver cancer)
	Hepatitis C virus (HCV)	Hepatocellular carcinoma, non-Hodgkin lymphoma
	Epstein-Barr virus (EBV)	Burkitt lymphoma, nasopharyngeal carcinoma, non-Hodgkin lymphoma, gastric carcinoma
	Kaposi sarcoma herpesvirus (KSHV)	Kaposi sarcoma, primary effusion lymphoma, multicentric Castleman disease
	Human T cell leukemia virus type 1 (HTLV-1)	Adult T-cell leukemia/lymphoma
	Merkel cell polyomavirus (MCPyV)	Merkel cell carcinoma (neuroendocrine skin cancer)
	Human immunodeficiency virus (HIV)	Various cancers
Parasites	*Schistosoma haematobium*	Bladder cancer
	Clonorchis sinensis and *Opisthorchis viverrini*	Cholangiocarcinoma (bile duct cancer)

might include the following aspects: (i) PAMPs mediated innate immune recognition; (ii) typical microbe-derived metabolites; (iii) with respect to host cell-microbe direct interactions, intracellular microbe induced autophagy and extracellular microbe triggered inflammation are two well-studied examples; (iv) the multi-faceted immunomodulation; (v) elicitation chemoresistance by influencing chemotherapeutics metabolism. Understanding the mechanisms underlying microbial effects within TME will bring new insight into anti-cancer therapy.

3.1. *PAMPs-mediated innate immune recognition*

PAMPs were first introduced in 1989 to describe conserved microbial components found in bacteria, viruses and fungi, but not in multicellular hosts, and recognized as foreign by pattern recognition receptors (PRRs) of innate immune system[169]. According to usual biochemical classification, microbial molecules bearing PAMPs are simply divided into lipids, proteins, carbohydrates and nucleic acids. Among them, lipopolysaccharide (LPS) is one of the most known PAMPs-bearing microbial molecules, which widely existed in most gram-negative bacteria[169]. Due to its robust induction of pro-inflammatory response, LPS is also referred to as Gram-negative bacterial endotoxin. Besides that, there are many other well-known microbial molecules bearing PAMPs, such as, porins found in bacteria, lipoteichoic acid found in Gram-positive bacteria, flagellin found in flagellated bacteria, hemagglutinin found in viruses, profilin-like molecule found in *Toxoplasma gondii*, mycobacterial glycoproteins found in *Mycobacteria*, ssRNA, dsRNA found in viruses, dsDNA found in bacteria and viruses, and hemozoin found in *Plasmodium*[169].

PRRs are membrane-associated or cytosolic evolutionary conserved receptors, mainly concentrated within Toll-like receptors (TLRs), C-type lectin receptors (CLRs), RIG-I-like receptors (RLRs) and NOD-like receptors (NLRs), each of them recognizes a fairly narrow set of PAMPs[170]. The recognition of PAMPs by the PRRs elicits intracellular signaling cascades in immune cells to express inflammatory mediators which ultimately trigger adaptive immune response, thus coordinate to modulate systemic immune responses. PAMPs-PRRs interactions are one of the key machineries to stimulate antitumoral or carcinogenic innate immune responses within TME, with emphasis on cancer immunology and immunotherapy[171]. Bacterial PAMPs can boost antitumor immunity by augmenting TLRs signaling and serving as cancer vaccine adjuvants[13]. Cancer vaccines functionalized with PAMPs could effectively reprogram suppressive TME to develop anti-tumor immune responses and immunological memory[172]. Fungi cell wall-derived PAMPs, *i.e.*, two β-(1,3)-glucans, are potent stimulators of mast cells activation, emphasizing the important role of mast cells in antifungal immunity[173]. However, aberrant or exaggerated activation of this fine-tuned PAMPs-PRRs interactions would lead to pathological inflammation, immunodeficiency or autoimmunity. Collectively, PAMPs derived from microorganism possess great ability in regulating TME and immune responses.

3.2. *Typical microbial metabolites-mediated interaction*

Messenger molecule-mediated interactions act as one of key machineries influencing cancer biology and tumor therapy, where messenger molecules fall into the following three broad types: (i) peptide toxins, (ii) secreted proteins and (iii) tumor microbiome-derived small molecule metabolites[13]. Studies showed small molecule metabolites were important modulators to maintain human physiology, regulate cellular metabolism as well as shape immune system, in either negative or positive ways within TME. There are two main categories of small molecule metabolites, *i.e.*, primary metabolites and secondary metabolites. The former is directly involved in the growth and development processes of organisms while the latter is not[174]. The typical primary metabolites biosynthesized by microbes are well-characterized, such as SCFAs, methylglyoxal (MGO), bile acids (BAs) and polyamines, some of which are directly related to host pathogenesis and carcinogenesis[168].

SCFAs are a subset of fatty acids and bi-products of bacterial fermentation, mainly consisting of acetate, propionate and butyrate. The highest levels of SCFAs are detected in the proximal colon, and acetogenic bacteria might contribute to 70% of acetate production in the colon, *Akkermansia muciniphila (A. muciniphila)* contributes to producing propionate production, Eubacteriaceae family and Ruminococcaceae family are known for butyrate production[175]. There are two well-identified SCFAs-mediated signaling mechanisms: (i) inhibition of histone deacetylases (HDACs) to regulate gene expression and (ii) activation of G-protein-coupled receptors (GPCRs), particularly GPR43 and

GPR41 to regulate metabolism, inflammation, and disease[176]. SCFAs might act as double-edged sword in tumorigenesis, which could exert both cancer-promoting or cancer-suppressing effects under different conditions, as studies showed, SCFAs are able to inhibit human colon cancer invasion while promote prostate cancer cells proliferation[177,178].

BAs are steroid derivatives presented predominantly in the bile, which could be further divided into primary BAs (*i.e.*, cholic acid and chenodeoxycholic acid) and secondary BAs (*i.e.*, deoxycholic acid and lithocholic acid), where primary BAs are synthesized by the liver while secondary BAs are derived from primary BAs by bacterial actions in the colon[179]. In spite of digestion functions, BAs also play essential regulatory roles in cancer development, especially secondary BAs, which have long been deemed to promote tumors[180]. It showed that lithocholic acid could induce endoplasmic reticulum stress and mitochondrial dysfunction in prostate cancer cell. And deoxycholic acid was found highly associated with CRC development, as the higher fecal concentration of deoxycholic acid, the higher incidence CRC[181,182].

Polyamines refers to small molecule metabolites with two or more amino groups, such as spermidine, putrescine and cadaverine produced by gut bacteria. Owing to their reducing activities, polyamines could protect cells from ROS, and they also possess the ability to modulate immune response by regulating macrophage polarization and function[183]. The roles of polyamines on cancer development are polyhedral and controversial, on one hand, polyamines could inhibit prostate cancer cells growth, however, on the other hand, it was also found increase the incidence of skin cancer[184,185].

MGO is a reactive carbonyl species generated endogenously during glycolysis. MGO displays potential cytotoxic, since it could react with nucleophilic groups of biological macromolecules, such as free amino groups of lysine and arginine in protein, as well as guanine residues in DNA or RNA[186,187]. DNA damages induced by reactive carbonyls, principally MGO, are referred to as DNA glycation, which could cause mutation, breaks in DNA and cytotoxicity. Additionally, MGO is also involved in the formation of advanced glycation end-products (AGEs). High levels of MGO are deleterious to cell survival, however, low levels of MGO are beneficial for cancer cell growth[188].

As for secondary metabolites, currently at least the following three examples have been well-established about their production sources, chemical structures as well as functions in cancer development: (i) colibactin, it is a genotoxic metabolite product by the members of Enterobacteriaceae family, especially pathogenic *E. coli*, and studies found colibactin has potential to motivate CRC development by inducing DNA double-strand breaks[189,190]; (ii) peptide aldehyde, produced by a series of microbes including but not limited to *E. coli*, *Streptomyces* and *Bacillus subtilis* species, shows great potential to increase carcinogenicity by inhibiting protease functions[191]; and (iii) thiopeptide, detected from many microbial species across various human bodies, such as *Enterococcus faecalis (E. faecalis)* in the gut, *Lactobacillus gasseri* in the urogenital tract, and *P. acnes* on the skin, it possesses strong antibacterial activities and might serve as anticancer agents by targeting proteasomes[192,193]. Collectively, microbial metabolites have exhibited direct or indirect impacts on cancer development, targeting tumor microbiome metabolism could not only provide better understand of tumor microbe microenvironment, but also offer novel therapy strategies for cancer treatment.

3.3. *Intracellular microbe induced autophagy*

Autophagy is a fundamental cellular homeostasis pathway that removes dysfunctional components through lysosome-dependent degradation and recycling[194]. Since many microbes invade into cells through internalization in phagosomes and endosomes, autophagy can also function as cell-autonomous antimicrobial defense against intracellular pathogens, which is in accord with the role of autophagy in cytoplasmic clean-up[195,196]. For example, one of the model systems reveals how autophagy cooperates traditional immunity system to defense intracellular pathogens is macrophage infection with *Mycobacterium tuberculosis (M. tuberculosis)*[197]. Additional examples about the microbes-elimination roles of autophagy also include Group A *Streptococci* which erode into interior of host cell, *Shigella* which escape from phagosome into the cytosol, and *Listeria* which employ pore-forming toxins to confront lumenal acidification to inhibit autophagic maturation[198,199].

As for the antimicrobial defense mechanism of autophagy, ever-increasing complex links existed between autophagy and well-established innate and adaptive immune systems, which might include but not limit to the following principles[197]: (i) autophagy serves as an immune effector of Th1/Th2 polarization, Th1 cytokines IFN-γ works on defense against intracellular pathogens *via* inducing autophagy, while Th2 cytokines, such as IL-4 and IL-13, inhibit autophagy and counteract IFN-γ induced autophagy, thus making cells accessible to intracellular pathogens; (ii) autophagy acts as immunological output effectors of PAMPs-PRR signaling, stimulating PRRs with PAMPs can induce autophagy, and TLRs activation can stimulate the autophagic elimination of *M. tuberculosis*; (iii) autophagy is an effector associated with immunity-related GTPases (IRGs) in regulating antimicrobial defense and inflammation, which are recognized as downstream of IFN-γ activation[200]. However, it is worth mentioning that some microbes have evolved strategies to avoided autophagy-mediated defense[201]. One strategy is modification of the endocytic compartments to prevent from fusion with lysosome, which allows the pathogen to escape from the endosomes, such as *Listeria* monocytogenes[202]. Another strategy is modification of the lysosomal environment, for example, *M. tuberculosis* employ this strategy to prevent acidification[198].

The interplay of autophagy and TME is intricate and paradoxical, autophagy might be double-edge sword in shaping TME according to distinct phases of tumor development[203]. Early in tumorigenesis with sufficient nutrient and oxygen supply, autophagy acts as a tumor suppressor *via* clearance of transformed cells and degradation of potentially oncogenic molecules. However, cytoprotective autophagy could fuel metabolic demands and sustain tumor cells survival in advanced tumor stages when facing nutrient deprivation, genotoxic stress and hypoxia, which might further favor cell motility and metastasis[204,205]. Moreover, autophagy is also involved in other cellular processes such as metabolic reprogramming, immune evasion, chemoresistance and tumor dormancy, which all contribute to tumor development.

3.4. *Tumor microbiome triggered pro-carcinogenic inflammation*

Inflammation is a protective or defensive action of host to harmful stimuli, especially defense against pathogens, which involves activation and participation of both innate and adaptive immunity[206].

Microbes, especially Gram-negative bacteria, possess intricate links to cancer-related inflammation, and serve as critical regulators of inflammation. With cumulative studies suggest an underlying microbes-mediated infectious component of cancer etiology; it is no exaggeration to say that inflammation act as a central facilitator in microbiota-related carcinogenesis[59]. As one proposed mechanistic framework stated, microbes exert a direct impact on tumor initiation *via* inflammation, per contra an indirect impact on tumor development, progression as well as therapeutic response, sharing interactions with other risk factors[59]. Specifically, microbes especially bacteria, could initially activate and perpetuate inflammatory responses, followed by enhancement of pro-inflammatory cells recruitment and cytokines secretion, accompanied with immune responses, which might result in oxidative stress imbalance, molecular alterations, oncogene mutations and neoplastic transformation, thus finally facilitate tumor progression and metastasis. Certainly, not all inflammation can promote carcinogenesis, depend on the condition and tumor types.

At the interfaces between microbiota and the host, there stand innate and adaptive immune response, where inflammatory cytokines are critical regulators of microbes and cancer interaction[207]. For example, it reported that the FadA and E-cadherin interaction-based host cell invasive functionality of *Fusobacterium* could elicit inflammation and drive production of the inflammatory cytokines IL-6, IL-8 and IL-18[208]. Additionally, it demonstrated that intratumor microbiota in CRC could trigger the activation of innate and adaptive immune cells infiltration, and elicit the secretion of tumor-promoting cytokines including TNF-α, TGF-β, IFN-γ, IL-18, IL-23 and IL-17, which are originally employed for combating infection, but also hijacked by tumor cells for survival[73,207]. Specifically, microbial PAMPs could activate TLRs and NLRs signaling upon infection, further lead to NF-κB and STAT-mediated inflammation and cytokine production. NLRP3/NLRP6 signals could activate IL-18 expression, dendritic cells (DCs) could sense bacterial components *via* TLR5 and produce IL-23, which could further promote the production of IL-17A and IL-22. If these cytokines are not controlled, it might turn into tumorigenesis[209]. On one hand, the cytokine expressions and inflammatory cell infiltrations are regulated by actions of commensal or pathogenic microbes, on the other hand, inflammation could also alter the composition and diversity of tumor microbiome and induces the expansion of microbes with cancer-promoting activities and genotoxic capabilities, thus making the host face a double hit system where both microbes-derived mediators and endogenous inflammatory mediators collectively promote tumorigenesis[210].

3.5. *The multi-faceted immunomodulation mediated by tumor microbiome*

Intra-tumor microbiota, act as new frontiers in tumor immunity, might exert a more powerful influence compare to body or gut microbiota due to their strong regional effect[68,211]. For example, intratumoral microbiota could exert an impact on cytokines production, which might elicit stronger immune response owing to higher local concentrations. The microbiota-produced highly conserved structural PAMPs, such as LPS and lipoproteins, could be recognized by PRRs in the first step to activate innate immune system. And afterwards, the adaptive immunity could be activated subsequently, which act as backbone of the antitumor response. $CD8^+$ T cells are one of the key components of adaptive immunity, and intratumoral microbiota can affect the infiltration of them[212]. For example, it showed that intratumoral bacteria where *Lachnoclostridium* genus ranked top could increase the migration and infiltration of cytotoxic $CD8^+$ T cells and benefit outcomes of patients with melanoma by regulating chemokine levels, such as CCL5, CXCL9 and CXCL10[115]. Additionally, Lam et al.[213] revealed that microbiota-induced IFN could program intratumoral antitumorigenic mononuclear phagocytes to promote anticancer immunity and immune checkpoint blockade efficacy, while absence of microbiota skewed TME toward pro-tumorigenic macrophages. Moreover, Ghaddar et al.[214] have identified a subset of tumor-associated bacteria that are associated with cancer hallmarks and immune activity, which could be employed to predict clinical prognosis and clinical management efficacy in pancreatic cancer.

On the other hand, intratumoral microbiota might also contribute to T cell incompetence and lead to immunosuppression *via* producing cytokines, upregulating immune check inhibitory points and recruiting immunosuppressive cells[211]. For example, it demonstrated that *Cutibacterium acnes* could contribute to an immunosuppressive TME in prostate cancer by inducing Treg infiltration and enhancing the effects of immunosuppressive mediators such as PD-L1, CCL17 and CCL18[215]. Additionally, IL-6 also plays a rather critical role in microbiota-induced tumor immunosuppression. It showed that LPS could promote IL-6 production through NF-κB signals, and then IL-6 would further activate JAK-STAT3 signaling to recruit MDSCs and increase PD-1 expression, thus mediating immunosuppression[216,217]. Moreover, microbial metabolites might also result in immunesuppression. Hezaveh et al.[218] demonstrated that *Lactobacillus*-produced tryptophan metabolites could activate the aryl hydrocarbon receptor (AhR) in tumor-associated macrophages (TAMs), which lead to rapid cancer progression and mortality in pancreatic cancer, while removal of dietary tryptophan could reduce TAMs AhR activity and inhibit tumor growth. Collectively, the intratumoral microbiota and their related products may both promote and suppress immunity, the immunomodulatory effects of intratumoral microbiota vary in different cancer types due to different microbiota compositions and distributions.

Based on the multitudinous effects of microbiota on tumor immunity, microbiota plays an important role in determining response to immunotherapy. Existing research have showed that the microbial communities colonizing the gastrointestinal tract can impact on the efficacy of anti-PD-1/L1 and anti-CTLA-4 therapies[219]. Besides gut microbiota, the profiles of intratumoral microbiota could also influence the responses of immunotherapy significantly. For example, Anker et al.[100] reported a patient-derived prostate-specific microbe, CP1, with local immunostimulatory properties, could be utilized to reprogram the "cold" TME and sensitize and the therapeutic efficacy of anti-PD-1 immunotherapy. As showed, CP1 could increase immunogenic cell death of cancer cells, induce infiltration of activated $CD8^+$ T cells, Th17 T cells, mature DCs, M1 TAMs, and NK cells, and meanwhile decrease Tregs and VEGF, thus resulting in strong clinical benefit in combination with PD-1 blockade. Intricate relationships exist between tumor microbes and tumor immune microenvironment (TIME)[220,221]. Although precise mechanisms of microbiome−immune interactions are yet to be elucidated, the underlying mechanisms of tumor microbiome-mediated multi-faceted immunomodulation might include but not be limited to following aspects: (i) microbial antigens, especially microbial antigens mimicry shared with tumor antigens, could potentially activate antitumor immune responses through valid presentation;

(ii) microbes-induced immunogenic cell death could effectively promote inflammatory TIME; (iii) microbe-derived metabolites could efficiently modulate TIME, and (iv) microbial adjuvanticity and PRRs-mediated signaling pathway could also modulate TIME[11].

3.6. Elicitation chemoresistance by influencing chemotherapeutics metabolism

There are three main influences of the resident microorganisms on chemotherapy: (i) facilitate therapeutic efficacy, (ii) abrogate and compromise anticancer effects, and (iii) elicit toxicity[222]. And the second type attracts most attention currently. Both the preclinical and clinical studies highlight the critical impacts of microbiome on tumor resistance to chemotherapeutic agents. Generally, the mechanisms of chemoresistance and chemotherapeutics inactivation might include but not limit to repair of damaged DNA, inhibition of programmed cell death, epigenetic changes, and altered gene amplification. More specifically, a mechanistic framework named TIMER (*i.e.*, translocation, immunomodulation, metabolism, enzymatic degradation, reduced diversity and ecological variation) has been proposed to help explain how intestinal microbiota influence the efficacies of chemotherapeutic drugs, including gemcitabine, 5-fluorouracil (5-FU), cyclophosphamide, irinotecan, platinum, oxaliplatin and methotrexate[222].

Similarly, recent studies also suggested the non-negligible effects of intra-tumor microbiota on the therapeutic responses of chemotherapy. For example, it reported that *F. nucleatum* could promote oxaliplatin chemoresistance in CRC, where *F. nucleatum* orchestrates microRNAs (mainly miR-4802 and miR-18a), TLRs, and autophagy network to control oxaliplatin resistance[223]. And intratumoral administration of *E. coli* to murine CT26 colon cancer model elicited chemoresistance to gemcitabine, also documenting the ability of local bacteria affect the efficacy of chemotherapeutic drugs[224]. Additionally, Geller et al.[64] reported that intratumor Gammaproteobacteria could metabolize gemcitabine into its inactive form (2′,2′-difluorodeoxyuridine) *via* expressing a long isoform of the bacterial enzyme cytidine deaminase (CDD_L) to elicit gemcitabine resistance, which could be abrogated by cotreatment with the antibiotic ciprofloxacin. Interestingly, 76% of PDAC also possess intratumoral Gammaproteobacteria (Enterobacteriaceae and Pseudomonadaceae families), which might account for one of the gemcitabine resistance mechanisms of PDAC[64]. Oppositely, the microbiome composition could be also modulated by gemcitabine treatment, the proportion of the two dominant phyla including Firmicutes and Bacteroidetes were significantly reduced after gemcitabine treatment, which shifted into Proteobacteria and Verrucomicrobia instead[225]. 5-FU, as a first-line CRC chemotherapeutic, is a potent inhibitor for *F. nucleatum*—a CRC associated detrimental bacterium, however, on the other hand, specific intratumoral microbiota members including *E. coli*, *B. fragilis*, *Bifidobacterium breve*, and *P. micra (P. micra)* are resistant to 5-FU and could modify it into a nontoxic form to deplete its efficacy and bioavailability, thus resulting in no ability to inhibit *F. nucleatum* and cancer development anymore[226]. Collectively, to improve understanding of how chemoresistance is driven by microbiomes could enhance the efficacy of current treatments, as the interplay between the intratumoral microbiota and chemotherapeutics is malleable, which could be modified or manipulated for individual treatment regime design of cancer patients.

4. Multidisciplinary approach-based interventions of tumor microbiome for cancer therapy

According to the basic features of tumor microbe microenvironment, strategies to intervene tumor microbiota for cancer therapy can divided into following aspects: (i) deleting harmful and cancer-causing microbiota species; (ii) in favor of beneficial microbiota, including adding beneficial bacterial species and modulating the existing commensal population; (iii) microbiota metabolites-based manipulation to reshape TIME; (iv) regulating microbiota to improve chemotherapy efficacy and (v) microbe-inspired drug delivery strategy for cancer therapy[227]. In any case, effective delivery of therapeutics, especially microbe-based therapeutics to the target site must be implemented appropriately by overcoming both environmental factors challenges (*e.g.*, acid, enzymes) and biological barriers (*e.g.*, mucus, existing microbiota)[228,229]. Multidisciplinary approaches that improve bioavailability, control transit and residence time, and target specific sites can help[230].

4.1. Targeted deletion of pro-tumoral microbiota species

4.1.1. Targeted delivery of antimicrobials

Both clinical and experimental evidence confirmed the existence of intratumoral bacterial, and clearing pathogenic bacterial is emerging therapeutic strategy for cancer treatment. Antibiotics administration remains as the major approach to fight against bacterial infection, while systemic distribution of antibiotics might result in a series of off-targeting side-effect, including imbalance of intestinal flora. To address these clinical challenges, Gao et al.[231] nanonized the antibiotic metronidazole by linking it with fluorouridine *via* disulfide bond linker to prepare an amphiphilic small molecule, which could self-assembled into nanoparticles and disassemble to release these two naïve drugs under high levels of glutathione in TME (Fig. 2A–C)[231]. The as-prepared platform could achieve synergistic antitumor effect by dual-target of both intratumoral microbiome and tumor cells, which could not only attack bacteria inside the tumor, but also re-shape TIME through clearance of bacteria and bacterial products, especially inactivating *F. nucleatum* related signaling pathways.

Nanoparticles with active targeted ability offer a feasible and powerful means to increase the therapeutic index of antibiotic[232]. Hussain et al.[233] prepared an antibiotic targeted delivery nanoparticle system by conjugating vancomycin-loaded porous silicon nanoparticles with a *Staphylococcus aureus (S. aureus)*-targeted cyclic 9-amino-acid peptide (*i.e.*, CARGGLKSC), which could specifically accumulate in *S. aureus* infected tissues with superior suppressive efficacy, thus decreasing both antibiotics dosage and drug resistance risk. *H. pylori* infection is the major cause responsible for inflammatory gastritis and gastric cancer, however, standard triple therapy exerted diminished potency due to antimicrobial resistance[234]. Unmet clinical needs in *H. pylori* eradication have drove the involvement of therapeutic nanoparticles, which can achieve concurrent delivery of multiple antibiotics, gastro-retentive properties, as well as site-specific targeted release kinetics, thus boosting local bactericidal efficacy while minishing systemic adverse effects meanwhile[235,236]. For example, inspired by the natural pathogen-host adhesion, Angsantikul at el[235].

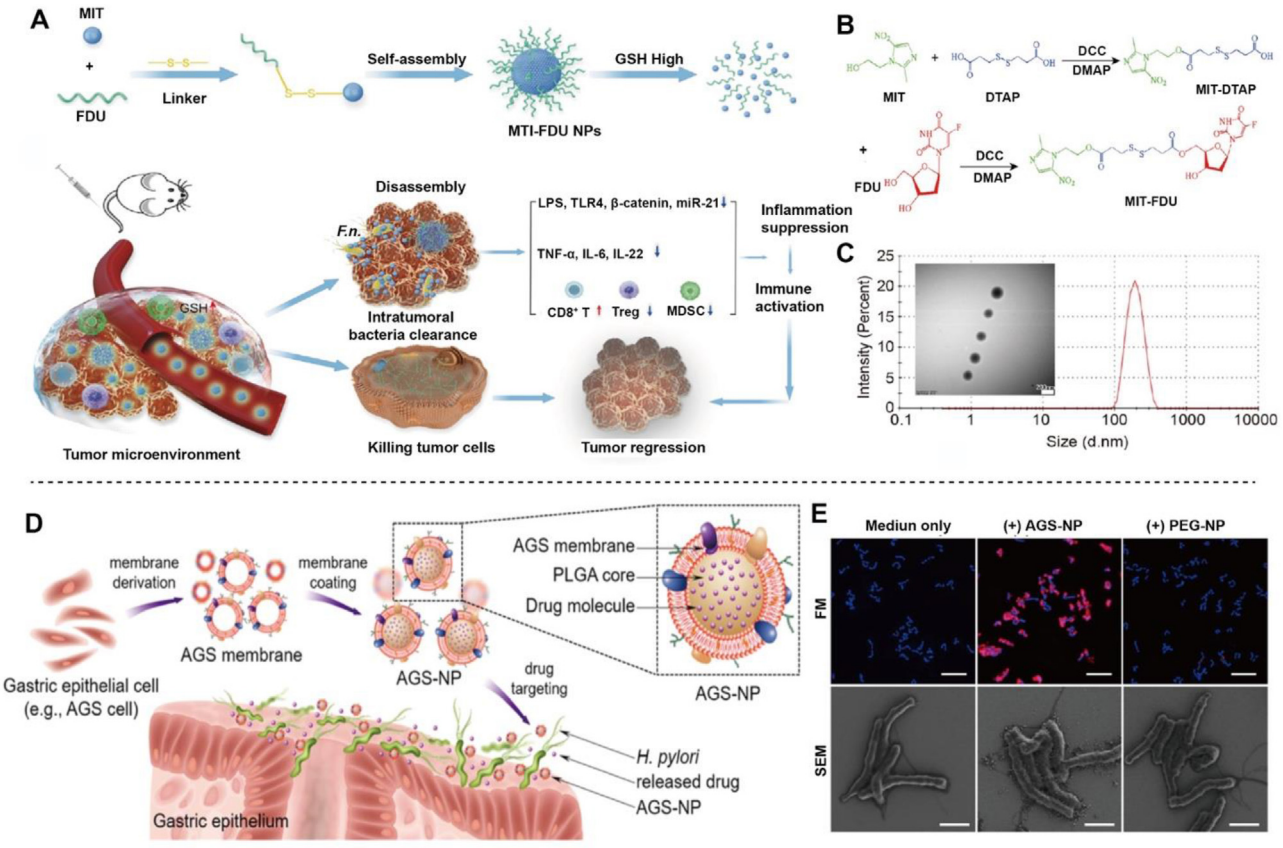

Figure 2 Representative examples of targeted delivery of antimicrobials. (A) schematic illustration of the preparation and therapeutic mechanism of tumor-targeting MTI-FDU nanoparticles, (B) synthetic routes and (C) particle size and TEM image of tumor-targeting MTI-FDU nanoparticles, reprinted with permission from Ref. 231. Copyright © 2023 American Chemical Society. (D) Schematic illustrations of gastric epithelial cell membrane-coated nanoparticles for targeted antibiotic delivery to treat *Helicobacter pylori* infection, (E) representative fluorescence-microscopy (FM) and SEM images, scale bar = 5 μm in FM and 1 μm in SEM, respectively, reprinted with permission from Ref. 235. Copyright © 2018 Wiley-VCH GmbH.sss

developed gastric epithelial cell membrane-coated clarithromycin loaded PLGA nanoparticles for targeted antibiotic delivery to eradicate *H. pylori* infection (Fig. 2D and E)[235]. The resulting biomimetic nanoparticles showed inherent adhesion and selective bind to the surfaces of *H. pylori*, thus achieving enhanced antibacterial efficacy. In addition, Hu et al.[237] reported another cloaked nanoparticle coated with platelet membranes, which displayed platelet-mimicking properties and enhanced binding to platelet-adhering pathogens (*i.e.*, methicillin-resistant *S. aureus*), and therefore, could be employed for targeted antibiotic delivery (*i.e.*, vancomycin). Moreover, novel environment-benign antimicrobial nanoparticles are prepared by infusing lignin nanoparticles with silver ions, and then coated with a cationic polyelectrolyte layer to promote bacterial adhesion[238]. The as-prepared nanoparticles could kill a broad spectrum of bacteria, including *E. coli* and *Pseudomonas aeruginosa (P. aeruginosa)*, with higher antimicrobial activity and smaller environmental impact.

4.1.2. Phage-based targeting deletion

Although antibiotics are employed as first-line and typical antibacterial treatment, their potency is limited by the diversity and complexity of microbial communities. The use of antibiotic has recently been linked to negative clinical outcomes due to drug resistance and adverse effects due to antibiotics would simultaneously remove both beneficial and harmful bacteria[229]. One potential alternative are phages, which could infect and lyse bacteria with accurate species-specific mechanism, exclusively removing enteric pathogens and meanwhile leaving beneficial strains alone[239,240]. With the abilities to edit, rather than destroy microbial communities, phage-based therapies attract plentiful research interests, some naïve or CRISPR-Cas armed phages are employed to destroy drug-resistant bacteria selectively while keeping the microbiome intact at the same time[241]. For example, Dedrick et al.[242] reported a clinical case about employing engineered bacteriophages to treat disseminated drug-resistant *Mycobacterium abscessus (M. abscessus)* in 15-year-old patient following bilateral lung transplantation. Intravenous phage treatment could effectively kill the infectious *M. abscessus* with objective clinical improvement.

Besides that, phage-mediated precise modulation of microbiota has achieved great success in various diseases treatment, including cancer[240]. For example, Duan et al.[243] found that cytolysin secreted by *E. faecalis* is a major cause of hepatocyte death and liver injury. Based on that, they developed a phage therapy to target against cytolytic *E. faecalis*, which is effective to abolish ethanol-induced liver disease. Moreover, Agarwal et al.[244] developed inhaled polymeric microparticles to facilitate the delivery of lytic bacteriophage to deep lung, which could

efficiently ameliorate acute lung infections by reducing *P. aeruginosa* populations. Given the detrimental impact and pro-tumoural roles of *F. nucleatum* in CRC, Zheng et al.[245] loaded a phage strain that could specifically lyse *F. nucleatum* into a biotic-abiotic hybrid nanosystem, which could significantly eliminate intra-tumoural *F. nucleatum* and augment the efficiency of CRC chemotherapy treatments. Compare to lytic phages, temperate phages incapable of replicating themselves might provide a safer option for phage display technology, since lytic phages might integrate their genome into the host cell to further potentially code resistance genes and release toxins[246,247]. Dong et al.[246] screened a specific *F. nucleatum*-binding M13 phage strain through temperate phage display *in vitro*, and silver nanoparticles were electrostatically assembled on the surface of M13 phages to form a phage-based bioinorganic hybridization system (M13@Ag). The as-prepared M13@Ag could selectively scavenge pro-tumor *F. nucleatum* and could further reverse immune-suppressive TME by blocking the recruitment of immunosuppressive cell (*i.e.*, MDSCs)[246]. Moreover, enhanced antitumor effects could be achieved when combined M13@Ag with immune checkpoint inhibitors or chemotherapeutics Besides microbiota modulation, phage also possess other means for cancer therapy, for example, Li et al.[248] genetically engineered a tumor-homing angiogenin-binding phage nanofibers to selectively suppress tumor angiogenesis by capturing angiogenin, demonstrating a general strategy of phage display-based breast cancer therapy. In spite of the excellent merits possessed by phage-based bacteria deletion therapies, their clinical translation might be limited owing to complicated purification, and characterization of phages. And pathogens may also become resistant to phage infection and lysis due to the complex evolutionary dynamics between phage and bacteria[229,249].

4.2. *In favor of beneficial microbiota species*

4.2.1. *Addition of beneficial bacterial species*

There are both pathogenic and beneficial microbiota within TME. Beneficial microbiota with abilities to initiate tumor-suppressive programs, are considered as our friends and could be employed as novel tools for anti-tumor therapy[250]. In favor of beneficial microbiota effects, there are typically two major approaches[227]: (i) addition of beneficial microbiota species, mainly bacteria which are called as probiotics, for example, *Clostridium butyricum* (*C. butyricum*) and *A. muciniphila* could produce anti-inflammatory SCFAs[251], certain *Bacilli* and *Clostridia* strains could inhibit pathogenic bacteria to protect intestinal health[252], and it showed that oral administration of *Bifidobacterium* could promote anti-tumor immunity and facilitate anti-PD-L1 efficacy[253]; and (ii) modulation of the existing commensal populations like fecal microbiota transplant (FMT) is another promising route, especially for CRC. However, FMT suffers limited development due to lack of operation standardization and inescapability of pathogenic bacteria. Similarly, significant challenges also remain microbial therapies, it will cause a certain degree of immune response and adverse effect in intravenous injection, conversely, the hostile gastrointestinal tract (*i.e.*, low pH, digestive enzymes, bile acids and agitation) will lead to undesired cell death and unsatisfactory therapeutic effect in oral administration[230].

Nanotechnology involving bulk encapsulation, single-cell encapsulation and surface decoration, could be adopted as a simple yet useful strategy to enhance the viability, bioavailability and functions of beneficial bacteria, which not only strengthen the resistance against environmental threats, but also endow bacteria with exogenous functions (Fig. 3A)[230,254,255]. For example, based on the protective roles of *Peptostreptococcus* against oral squamous cell carcinoma, Zheng et al.[256] reported intratumoral delivery bacterium *P. anaerobius* to upregulate *Peptostreptococcus* levels, alongside subcutaneous delivery of a silver nanoparticles loaded adhesive hydrogel to inhibit other harmful bacteria, could synergistically achieve enhanced anti-tumor responses. However, bulk encapsulation usually suffers a series of limitations, like uncontrollable particle size, unavoidable cell leakage and limited *in vivo* colonization, which might be overcome by single-cell encapsulation strategy. Xie et al.[257] reported a prebiotic-based single-cell encapsulation strategy of *E. coli Nissle 1917* (EcN) to resist gastrointestinal stresses, where single EcN was armed with a "shield" composed by Fe^{3+}-tannic acid cross-linking network and carboxymethylated β-glucan (Fig. 3B)[257]. Centurion et al.[258] also demonstrated a cell-mediated catalytic bio-interfacial phenolic assembly to form protective nano-shells on individual therapeutic bacteria, which was achieved by oxidative polymerization and film formation of phenolic compounds with assistance of an essential nutrient (manganese) of the probiotics, without any additional chemical modification step (Fig. 3C and D)[258].

Surface modifications, especially single-cell decoration, are important approach to confer microbial therapies with new properties and features, and meanwhile reserve the biological functionalities of the key elements on the surface of microbiota, such as inherent antigens and flagella for communication, interaction and adhesion[230]. For example, Vargason et al.[259] developed bio-inspired technologies to rapidly modify therapeutic bacteria with synthetic adhesins to facilitate its targeted colonization, based on the specific interactions between the bacteria and its adhesion target. Additionally, Cao et al.[260] reported an artificial-enzymes-armed *Bifidobacterium longum (B. longum)* probiotics, which decorated artificial enzymes to the surfaces of *B. longum via* C18-PEG-B linker through click reaction. The artificial enzyme is a type of nanomaterial that contains atomically dispersed active metal centers, which could mimic natural antioxidant defense systems to protect *B. longum* from oxidative damage, thus improving bacterial viability and shaping the gut microbiota towards a beneficial state. Although some research examples of bacteria delivery mentioned above aren't designed for cancer therapy, the involved strategies might have great reference significance.

4.2.2. *Modulation of the existing commensal population*

Modulation of the existing commensal population can also exert therapeutic effects to various diseases. For example, Zheng et al.[261] constructed an effective and biocompatible microbiota-modulating prebiotics-encapsulated probiotic spores (spores-dex) *via* host−guest interaction between adamantine modified *C. butyricum* and β-cyclodextrin modified prebiotic dextran (Fig. 3E and F)[261]. After oral administration, the prepared spores-dex can enrich in colon cancers specifically, where dextran could be fermented by *C. butyricum* to produce anti-cancer SCFAs, and further augment the abundance of other SCFAs-producing bacteria, such as *Eubacterium* and *Roseburia*, which could systematically regulate gut microbiota and suppress colon cancers. Lee et al.[262] reported a novel kind of nano-aggregation formed by an amphiphilic conjugate between hyaluronic acid (HA) and bilirubin, which could accumulate in inflamed colonic epithelium,

and modulate the overall richness and diversity of gut microbiota. Specifically, the abundance of *A. muciniphila* and *Clostridium XIVα* were markedly augmented to maintain gut homeostasis. Additionally, Ouyang et al.[263] innovated an oral hydrogel microbeads-based biochemical strategy for *in situ* synthesis of selenoproteins to regulate microbiota composition, which prepared by coating hyaluronic acid-modified selenium nanoparticles with a shell of calcium alginate hydrogel. The as-prepared hydrogel microbeads could increase the probiotics abundance, and suppress detrimental communities to maintain intestinal homeostasis. Chen et al.[264] reported a kind of natural exosome-like nanovesicles from edible tea flowers, which contain large amounts of polyphenols, flavonoids, functional proteins, and lipids, could effectively suppress metastatic breast cancer, partially owing to gut microbiota modulation by maintaining the abundance of the typical beneficial symbiotic bacteria. In conclusion, manipulation of both intestinal microbiome and intratumoral microbiota has great potential to reduce the incidence and severity of a wide range of human conditions and diseases[228].

4.3. *Microbiota metabolites-based intervention to reshape TME*

4.3.1. *Typical microbial metabolites-mediated therapy*

SCFAs, as a collection of carboxylic acids produced by gut microbiome fermentation, possess versatile therapeutic effects against various cancers, while their clinical translation is limited by rapid renal clearance and high dose-based side effects[265]. Based on that, Shashni et al.[266] prepared a new amphiphilic block

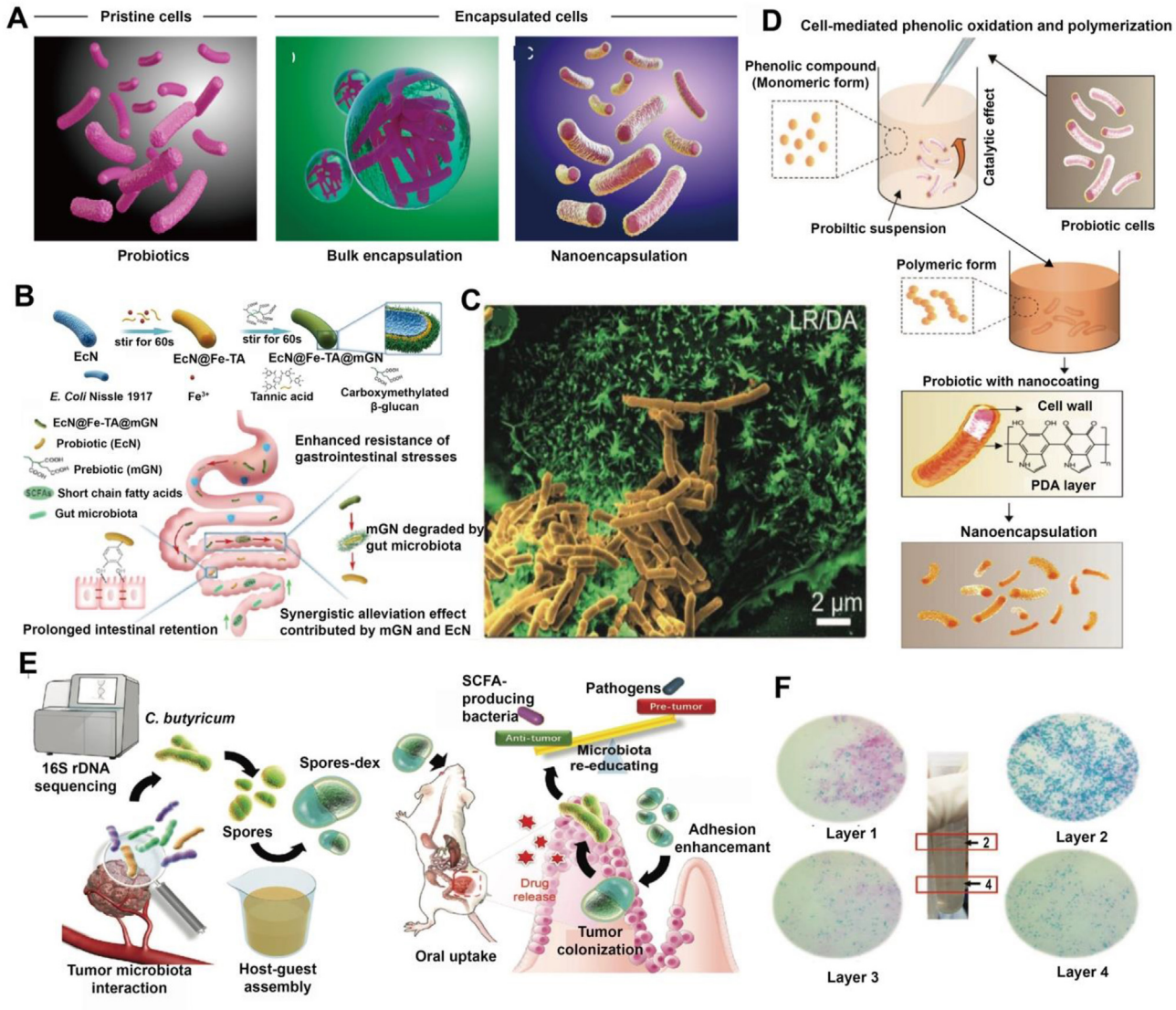

Figure 3 Representative examples of nanotechnology-based in favor of beneficial microbiota species (A) schematic of bulk encapsulation and nanoencapsulation, reprinted with permission from Ref. 255. Copyright © 2021 American Chemical Society. (B) Schematic illustration of the preparation and therapeutic mechanism of modified prebiotic-based "shield" armed probiotics, reprinted with permission from Ref. 261. Copyright © 2023 American Chemical Society. (C) SEM images of polydopamine-coated probiotic adherence to Caco-2 cells and (D) schematic process of cell-mediated oxidation of catechol compounds and *in situ* nanoencapsulation, reprinted with permission from Ref. 258. Copyright © 2022 Wiley-VCH GmbH. (E) Illustration of the prebiotics-encapsulated probiotics to regulate gut microbiota and suppress colon cancer, and (F) separation of spores by density gradient centrifugation, reprinted with permission from Ref. 261. Copyright © 2020 Wiley-VCH GmbH.

copolymer-based SCFAs prodrugs by covalently conjugating SCFAs (*i.e.*, butyric acid or propionic acid) to hydrophobic polymer segment *via* ester linkages, which could self-assemble into orally administrable nanoparticles and effectively retard the growth and metastatic potential of melanoma tumors. LPS, as one of the most prevalent products of Gram-negative microbiota, is a well-known immune-stimulatory ligand. However, LPS is also found to promote intestinal inflammation and CRC progression *via* activating TLR4 and NF-κB pathways[267]. Therefore, Song et al.[268] engineered an LPS-targeting fusion protein, and loaded its coding sequence into a lipid-protamine-DNA (LPD) nanoparticle system to selectively block LPS signal within TME by *in situ* expression of LPS trap protein, which could significantly boost anti-PD-L1 therapy by relieving immunosuppressive TME. Primary BAs produced in liver are metabolized to secondary BAs by intestinal bacteria, and dysregulated BAs (*i.e.*, decreased primary BAs and elevated secondary BAs) closely linked to liver carcinogenesis. Ji et al.[269] propose a nano-approach to modulate BAs signaling by intravenous delivery BAs receptor modulators for liver cancer immunotherapy, where obeticholic acid (*i.e.*, primary BAs receptor agonist) and 5β-cholanic acid 3 (*i.e.*, secondary BAs receptor antagonist) were loaded into a polyoxazole-based nanosystem separately. The as-prepared formulations could elicit robust T cell-mediated immunotherapy against liver cancer.

Moreover, recent studies showed that D-lactate, a gut microbiome small-molecule metabolite, could program Kupffer cells to capture and kill circulating pathogens after reaching liver *via* the portal vein[270]. Han et al.[271] found that D-lactate could transform immunosuppressive M2 TAMs into M1 phenotype through modulation of PI3K/Akt and NF-κB pathway. Based on that, they designed a kind of D-lactate-loaded biomimetic targeted PLGA nanoparticles to remodel immunosuppressive TME, which further substantiates the TAMs modulatory function of D-lactate and provides a combinatorial strategy for hepatocellular carcinoma immunotherapy. Moreover, Mager et al.[272] reported that inosine, an immunotherapy-promoting metabolite produced by *Bifidobacterium pseudolongum*, could promote T_H1 activation and enhance checkpoint inhibitor immunotherapy, with potential to be exploited to develop microbial-based adjuvant therapies.

4.3.2. *Microbiota-derived products-mediated therapy*

In addition to these well-known typical microbial metabolites, bacterial flagellin secreted by engineered bacteria is another potential candidate to reshape TME for cancer treatment[273]. Zheng et al.[274] engineered an attenuated *Salmonella typhimurium (S. typhimurium)* strain to overexpress and secrete a heterologous bacterial *Vibrio vulnificus flagellin* B (FlaB), which acted as an admirable immunotherapy adjuvant through activating innate immune responses *via* TLR5 pathway. It showed that the engineered FlaB-secreting bacteria could effectively suppress tumor growth *via* two-step cooperative mechanism, firstly, the TME colonization and proliferation of engineered *Salmonella* could induce abundant immune cells infiltration (*i.e.*, TAMs, monocytes and neutrophils) by activating TLR4 signaling *via* LPS, subsequently, the secreted FlaB could further activate recruited immune cells through TLR5 signaling and modulate TAMs into M1 phenotypes to amplify tumor-suppressive efficacy. Besides that, Griffin et al.[275] also reported a novel kind of immunotherapy adjuvant, *i.e.*, *Enterococci* with specialized peptidoglycan remodeling abilities, which could secrete the NlpC/p60 peptidoglycan hydrolase SagA orthologs to generate immune-active muropeptides to promote checkpoint inhibitor cancer immunotherapy.

4.4. *Targeted regulating microbiota to improve chemotherapy efficacy*

4.4.1. *Reversing bacteria-mediated gemcitabine resistance*

Growing studies suggest that microbiome can impair chemotherapy efficacy by metabolizing chemotherapeutic agents, while nanotechnologies might provide innovative strategies to reverse it due to their potential to manipulate the interaction between microbiome and TME. One of the most typical examples is gemcitabine, intratumor Gammaproteobacteria can metabolize it into its inactive form, while their metabolic effect was greatly dependent on the CDD_L expression[64,276]. Co-treated with antibiotics such as ciprofloxacin and colistin is a feasible approach to abrogate gemcitabine resistance. For example, Qiu et al.[277] developed colistin and gemcitabine co-delivery micelles (termed CCGM), where gemcitabine was chemically linked with a self-immolative linker and then conjugated to Pluronic F127, and colistin was employed as a crosslinker to make colistin-crosslinked gemcitabine micelles (Fig. 4A)[277]. And colistin and gemcitabine could be released on demand in TME to inhibit bacterial growth and simultaneously treat the tumor[277]. Although co-delivery with antibiotics could potentiate the antitumor efficacy of gemcitabine, overuse of antibiotics is not recommended owing to antimicrobial resistance. Instead, inhibiting CDD_L activity could be an excellent alternative therapeutic strategy. For example, Xi et al.[278] reported that nitrogen-doped carbon nanospheres (N-CSs) could act as nano-inhibitors of CDD_L to overcome bacteria-mediated gemcitabine resistance, where the nitrogen-doped graphitized structure of the N-CSs could competitively bind to the active center of CDD_L. It showed that the N-CSs could successfully reverse CDD_L-induced gemcitabine resistance and restore tumor susceptibility to gemcitabine. Moreover, the N-CSs also possess peroxidase-like activity to catalyze H_2O_2 into $\cdot OH$ radicals for tumor catalytic therapy, thus synergizing gemcitabine chemotherapy with nanozyme-mediated catalytic therapy to achieve effective tumor treatment (Fig. 4B)[278].

4.4.2. *Overcoming F. nucleatum-mediated chemoresistance*

F. nucleatum is well-known to drive pro-tumoral TME, which has been widely implicated in CRC and directly involved in chemoresistance[223,279,280]. 5-FU based chemotherapy is the first-line treatment for advanced CRC, however, recent studies demonstrated that *F. nucleatum* could promote chemoresistance to 5-FU in CRC, which directly lead to therapy failure[223,280]. Therefore, it's critical to inhibit or deplete *F. nucleatum* in colon for 5-FU based chemotherapy. Chen et al.[281] developed a combination strategy cooperating metronidazole (MTX) based microbiota modulation and 5-FU based chemotherapy, where antibiotic MTZ and 5-FU were individually loaded into metal polyphenol network-coated mesoporous silica nanoparticle (MSN), and then blended with carboxymethyl cellulose (CMC) to obtain a therapeutic gel. The as-prepared gel could enhance chemotherapy efficacy by the elimination of *F. nucleatum,* hereby effectively inhibiting the tumor growth (Fig. 4C)[281].

Although antibiotics elicited *F. nucleatum* inhibition is advantageous for CRC chemotherapy, antibiotic therapy lacking tumor-targeting will lead to the gut microflora disturbance because of non-selective deletion of both pro-tumoral and antineoplastic bacteria. Therefore, a safe and controllable alternative antibiotic treatment is highly desirable. Based on the excellent elimination ability of lauric acid (LA) to *F. nucleatum*, Yan et al.[282] prepared a multifaceted supramolecular nanomedicine by conjugating LA

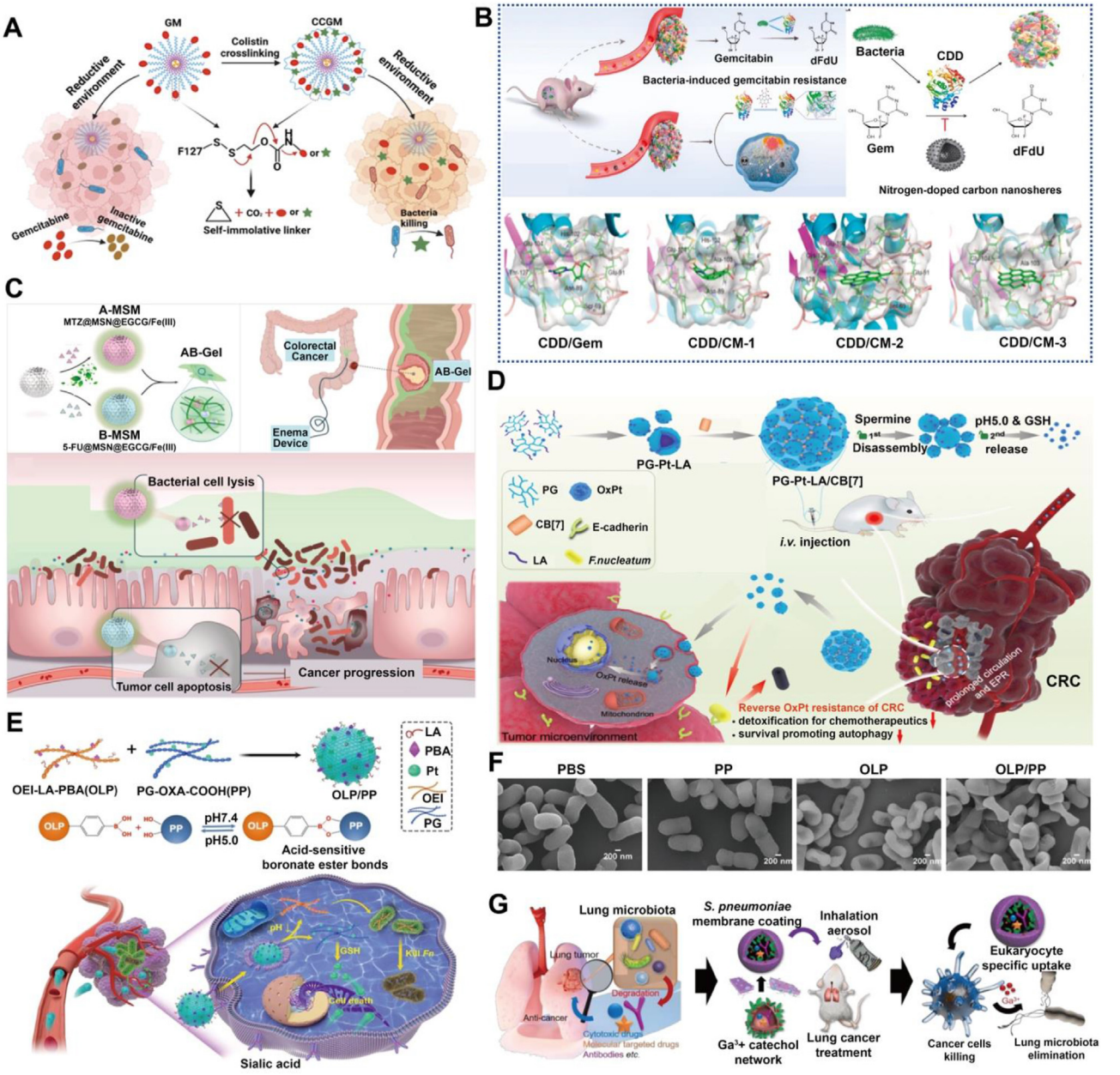

Figure 4 Representative examples of targeted regulating microbiota to improve chemotherapy efficacy. (A) Schematic illustration of colistin crosslinked gemcitabine micelle eliminating bacteria-induced cancer drug resistance, reprinted with permission from Ref. 277. Copyright © 2022 American Chemical Society. (B) Schematic illustration of the strategy using nanozyme-mediated catalytic therapy to overcome tumor drug-resistance induced by intratumor bacteria, and the related molecular dynamic (MD) simulations, reprinted with permission from Ref. 278. Copyright © 2022 Elsevier. (C) Schematic illustration of the preparation and therapeutic mechanism of the prepared tumor-triggered release drug delivery gel, reprinted with permission from Ref. 281. Copyright © 2021 Elsevier. (D) Schematic illustration of supramolecular nanomedicine for enhanced chemotherapy to treat CRC, reprinted with permission from Ref. 282. Copyright © 2022 Elsevier. (E) Chemical structure and molecular design of the tumor-targeting nano-assembly, and (F) SEM images of *Fusobacterium nucleatum* after different treatments, reprinted with permission from Ref. 283. Copyright © 2023 American Chemical Society. (G) Depletion of lung microbiota with bioinspired nanomedicine for improving lung cancer chemotherapy, reprinted with permission from Ref. 287. Copyright © 2023 American Chemical Society.

and platinum (IV) oxaliplatin prodrug to hyperbranched polyglycidyl ether, with addition of cucurbituril elicit supramolecular assembly, which substantially promoted the chemotherapeutic efficacy (Fig. 4D)[282]. Similarly, Li et al.[283] constructed an active tumor-targeting acidity-responsive nano-assembly to enhance CRC chemotherapy by employing LA, where LA and phenylboric acid were conjugated to oligomethyleneimine, followed by interaction with oxaliplatin prodrug-modified polyglycidyl ether to obtain nano-assembly (Fig. 4E and F)[283]. Through the on-site drug delivery, the nano-assembly could specifically target the tumor cell, and efficiently eliminate tumor-resident *F. nucleatum* to overcome chemoresistance and significantly inhibit tumor growth.

Additionally, by virtue of the targeting specificity of phages to bacteria, phage-guided microbiota elimination might also be suitable strategies to reverse chemo-resistance by accurately removing certain bacteria. Accordingly, Zheng et al.[245] reported a phage-guided strategy to augment chemotherapy responses in CRC models, where they firstly isolated a phage strain with ability to specifically lyse *F. nucleatum*, and then linked the azide-modified phages with functionalized irinotecan loaded dextran nanoparticles, finally yielding a phage-guided biotic−abiotic hybrid nanosystem. It showed that the prepared nanosystem could highly accumulated in tumors, effectively eliminated intratumoural *F. nucleatum*, and significantly augmented the efficiency of first-line chemotherapy treatments of CRC.

4.4.3. *Abrogating chemoresistance by metal ion-based antibacterial materials*

Moreover, metal ion-based antibacterial materials such as Ag^{+}, Zn^{2+}, Ga^{3+}, showing promising antibacterial potentials with favorable safety, could also employed as potent alternative for antibiotics[284]. Among them, Ga^{3+} could effectively inactivate diversiform microbes by disrupting bacterial iron metabolism[285,286]. Based on that, Han et al.[287] reported an inhalable microbial capsular polysaccharide camouflaged etoposide-loaded Ga^{3+}-based metal−organic network to abrogate bacteria-induced chemoresistance by depleting local lung microbiota, which showed excellent antimicrobial ability and enhanced anti-tumor efficacy (Fig. 4G)[287]. In all, we have summarized several microbiota-depleted nano-strategy to overcome chemoresistance by inhibiting microbial inactivation of therapeutic drugs in TME.

4.5. *Microbe-inspired tumor-specific strategy for cancer therapy*

4.5.1. *Genetically engineered microbiota for cancer therapy*

With development of synthetic biology, genetic engineering approaches have been widely utilized to fabricate bacteria-based artificial expression and release of therapeutic payloads for tumor treatment, due to the selective and preferential colonization of bacteria within hypoxic and necrotic TME[288]. In this technology,

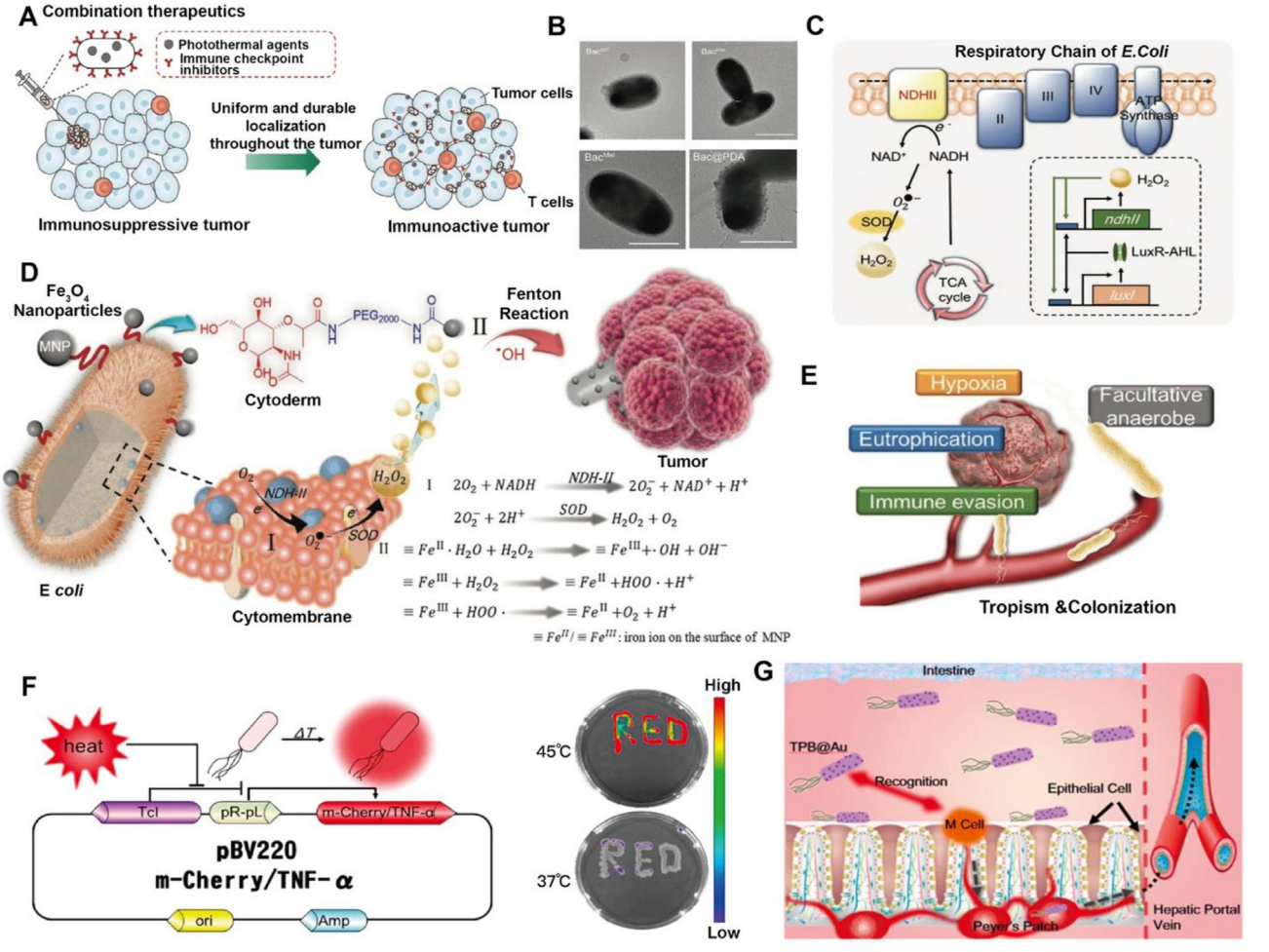

Figure 5 Representative examples of genetically engineered microbiota for cancer therapy. (A) Schematic illustration of spatiotemporally controllable distribution of combination therapeutics in solid tumors, and (B) representative TEM images of Bac^{WT}, Bac^{Mel} and Bac@PDA respectively, Scale bar = 1 μm, reprinted with permission from Ref. 291. Copyright © 2021 Wiley-VCH GmbH. (C) Mechanism of NDH-2 expression based on synthetic biology. (D) Scheme of bacteria-based Fenton-like bioreactor and (E) illustration of bacterial tropism and colonization in tumor regions, reprinted with permission from Ref. 293. Copyright © 2019 Wiley-VCH GmbH. (F) Mechanism and expression of m-Cherry/TNF-α expression based on plasmid pBV220, and (G) speculated scheme of oral administration route for delivery, reprinted with permission from Ref. 294. Copyright © 2018 American Chemical Society.

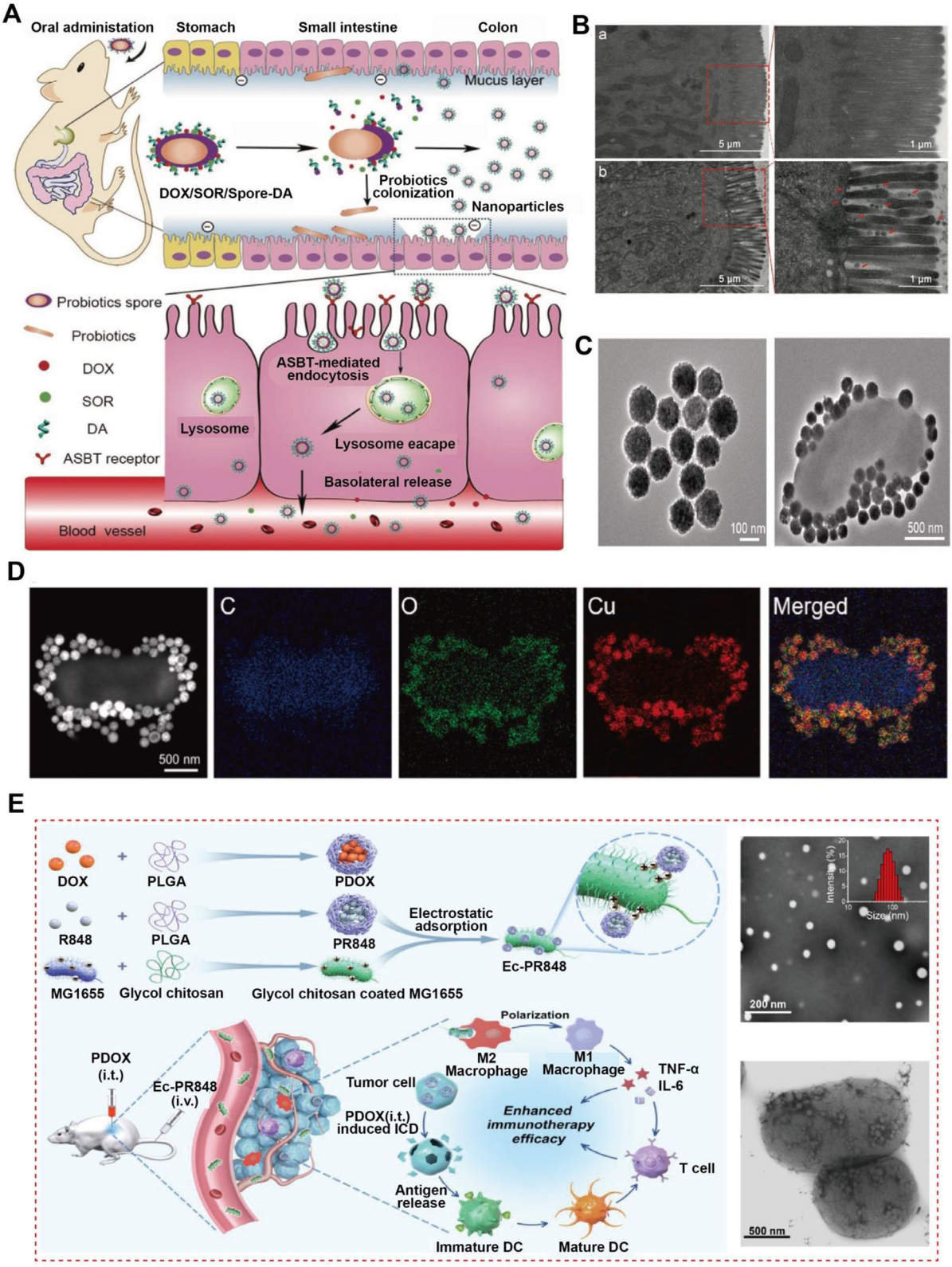

Figure 6 Representative examples of microbiota-based bioactive materials for drug delivery. (A and B) schematic illustration of oral autonomous biological nanogenerator in the intestine and representative TEM images of intestinal tissue uptake, reprinted with permission from Ref. 297. Copyright © 2019 Wiley-VCH GmbH. (C) Representative TEM images of Cu_2O nanoparticles and Bac@Cu_2O biotuner, and (D) Element mapping images of Bac@Cu_2O biotuner, reprinted with permission from Ref. 298. Copyright © 2022 Elsevier Ltd. (E) Schematic illustration of the fabrication and therapeutic mechanism of nanoparticles/bacteria complex, and their related TEM images, reprinted with permission from Ref. 301. Copyright © 2021 American Chemical Society.

customized plasmids are transfected into bacteria, which control the synthesis of target proteins. Based on this technology, bacteria producing nanobodies (*i.e.*, CD47, PD-L1 and CTLA-4) have been engineered for tumor therapy *via in situ* expression, which could achieve local delivery of higher effective therapeutic concentrations with lower systemic side effects. For example, to avoid severe side effect cause by unwanted CD47 blockade of red blood cells and platelets, Chowdhury et al.[289] reported a non-pathogenic *E. coli* strain, which could undergo intratumoral quorum lysis within TME owing to the production of a bacteriophage lysis protein (φX174E), and subsequently release an encoded nanobody antagonist of CD47 to induce systemic antitumor immunity and durable tumor regression by activating of tumor-infiltrating T cells. Additionally, to circumvent the immune-related adverse effects of anti-PD-L1 and anti-CTLA-4 combination therapies, Gurbatri et al.[290] constructed a kind of engineered probiotics for tumor-specific local delivery of checkpoint blockade nanobodies by transfecting plasmid into EcN to express and release both PD-L1 and CTLA-4 antagonistic nanobodies using a *LUXL* and *φX174E* genes-dependent lysing release mechanism. And the engineered system demonstrated enhanced therapeutic response and significant tumor regression harnessing the converging advancements in both immunotherapy and synthetic biology.

To disperse antitumor drugs homogenously throughout an entire solid tumor, Wang et al.[291] constructed a photothermal melanin-expressing bacteria by transforming a plasmid DNA encoding tyrosinase into an *E. coli* strain, which could distribute uniformly within tumors due to their nature to colonize the hypoxia intratumoral environment, and generate an efficient heating of the tumor upon light exposure (Fig. 5A and B)[291]. Under 808 nm laser irradiation, the temperature of engineered bacteria could be controlled flexibly in a range of 40−55 °C by adjusting their concentration (from 1.25×10^6 to 5×10^6) with 90 s, suggesting their highly efficient photothermal conversion abilities. And further attaching αPD-1 on the surface of engineered bacteria would result in synergistical therapeutic efficacy by eliciting a dually photothermally stimulated and checkpoint-blockade-mediated immune activation effect, thus significantly inhibiting tumor growth.

Based on key determinant of L-arginine on anti-tumour T cell response and cooperative role of L-arginine with PD-L1 blockade, Canale et al.[292] developed an engineered probiotic EcN strain by deleting the arginine repressor gene (ArgR), which could effectively colonize within tumor and converts ammonia into L-arginine. And the as-engineered bacteria could effectively enable metabolic modulation of TME, thus resulting in enhanced efficacy of immunotherapies. Additionally, modification engineered bacteria with functional nanoparticles will further optimize their anti-tumor efficacy. For example, Fan et al.[293] reported an integrative bacterial bioreactor by decorating magnetic Fe_3O_4 nanoparticles onto the surface of nonpathogenic bacterium *E. coli MG1655* which was engineered to overexpress respiratory chain enzyme II (NDH-2) (Fig. 5C−E)[293]. And the constructed bioreactor could specifically colonize in tumor regions, where NDH-2 could increase localized H_2O_2 generation, and Fe_3O_4 nanoparticles could further convert H_2O_2 into toxic hydroxyl radicals (•OH) *via* Fenton-like reaction to induce tumor cell death. This research group also reported another orally-administrated thermally sensitive programmable bacteria, where *E. coli MG1655* was transformed with custom-designed plasmid pBV220 containing a thermally sensitive promoter and the gene of TNF-α to achieve thermally sensitive expression of TNF-α, with aid of photothermal gold nanoparticles decorated on their surface to generate heat under near-infrared light irradiation. The as-designed system could achieve a robust expression of TNF-α after incubation at 45 °C for 10 min (Fig. 5F and G)[294].

Besides bacteria, other microbiota such as virus could also be employed to express and secrete therapeutics within TME for cancer therapy. For example, Wang et al.[295] generated an engineered oncolytic vaccinia virus co-expressing PD-L1 inhibitor and granulocyte-macrophage colony-stimulating factor (GM-CSF), which could effectively activate tumor neoantigen-specific T cell responses due to synergistic action of viral replication, PD-L1 blockade as well as GM-CSF stimulation, thus leading to effective rejection of both virus-injected and distant tumors.

4.5.2. *Microbe-inspired hitchhiking for tumor-targeting*

Due to the excellent tumor target and penetration abilities of *Salmonella enterica serovar* Typhimurium VNP20009, Suh et al.[296] developed a novel kind of bacteria-enabled autonomous platform by loading PLGA nanoparticles to the outer membrane of the bacteria *via* streptavidin−biotin interaction, which could effectively delivery nanotherapeutics into poorly vascularized tumor tissue relying on bacteria translocation and proliferation mechanism, with enhanced tumor accumulation even up to a remarkable 100-fold[296]. Additionally, inspired by the disintegration of hydrophobic protein coat in the intestinal microenvironment of spores, Song et al.[297] developed oral autonomous biological nanogenerator by modifying spores (*i.e.*, *Bacillus cagulans*) with deoxycholic acid and loading with chemotherapeutic drugs (*i.e.*, doxorubicin and sorafenib), which could autonomously produce substantial nanoparticles in the intestine to increase drug penetration and absorption (Fig. 6A and B)[297]. On account of the instinctive *Eubacterium hallii (E. hallii)* -driven tumor tropism, Liang et al.[298] designed a "turn-bads-to-goods" biotuner by integrating Cu_2O nanoparticles with *E. hallii* based on electrostatic interaction, which could actively accumulate in CRC (Fig. 6C and D)[298]. On one hand, the as-prepared biotuner could mediate Fenton-like reaction to produce cytotoxicity ·OH *via* interaction between Cu_2O and endogenously overexpressed H_2S, on the other hand, the colonized *E. hallii* could generate more beneficial SCFAs, thus boosting anti-tumor efficiency.

Additionally, Chen et al.[299] leveraged the tumor-targeting ability of *Salmonella* strain VNP20009 with polydopamine-mediated photothermal therapy by coating polydopamine on the surface of bacteria *via* oxidation and self-polymerization. After intravenous injection, tumor temperature could reach up to 55 °C within 5 min of laser irradiation, thus resulting in a superior anticancer effect against melanoma. Moreover, Zheng et al.[300] reported a new kind of living photosynthetic bacteria *Rhodobacter johrii*, which could be employed for hypoxia-targeted cancer therapy with no post-modification, due to their naïve facultative aerobes, near-infrared (NIR) chemotaxis and photothermal properties in an "all in one" manner[300]. Wei et al.[301] developed a kind of nanoparticles/bacteria complex for TAMs polarization therapy by attaching toll-like receptor 7/8 agonist resiquimod-loaded PLGA nanoparticles onto the surface of *E. coli MG1655 via* electrostatic absorption, which could greatly polarize M2 TAMs to M1 type (Fig. 6E)[301]. And immunogenic cell death could be induced by when combined with doxorubicin-loaded PLGA nanoparticles to commendably enhance the efficacy of immunotherapy.

Despite the preferential colonization of bacteria with tumor sites attributed to anaerobic, eutrophication, and immunosuppressive

TME, bacterial-mediated biotherapies still suffer insufficient targeted abilities and low treatment efficacy. Therefore, strategies to increase the tumor-targeting capacity of bacteria are highly desired, which will greatly benefit for antitumor efficacy. Due to the favorable features of aptamers (*i.e.*, high affinity, excellent specificity and easily synthesis), Geng et al.[302] reported an aptamer-assisted strategy to promote tumor localization of bacteria by simply conjugating aptamers to bacterial surface *via* amidation reaction, where an optimal number of 2.8×10^5 aptamers per cell present the highest specificity to tumor cells *in vitro*, as it could generate about 2- and 4-times higher local accumulation in tumors compared to unmodified bacteria at 12 and 60 h. Based on that, aptamer-conjugated attenuated *S. typhimurium* exerted significantly enhanced antitumor efficacy *in vivo*.

4.5.3. OMVs-based nanoplatform for drug delivery

Bacterial outer membrane vesicles (OMVs), are derived from Gram-negative bacteria by blebbing of the outer membrane, and characterized with nano-sized lipid bi-layered vesicular structures enriched with multiple parent bacteria-derived components[303].OMVs are excellent candidate for non-living vaccines, adjuvants, drug delivery vehicles and cancer immunotherapy agents based on their intrinsic possession of PAMPs, bacterial antigens, adhesins and various proteins[16].

OMVs represent an interesting vaccine platform, not only for their built-in adjuvanticity and simplicity of production process, but they can also be easily decorated with foreign antigens *via* different synthetic biology approaches. It is worth mentioning that, Bexsero, composed by detergent-extracted OMVs and three recombinant proteins, is a licensed and clinical-approved OMVs-based vaccine for meningococcal group B vaccine in children, demonstrating the great clinical-transformation prospects of OMVs. In the field of basic research, Cheng et al.[304] reported a flexible OMVs based vaccine platform to display tumor antigens onto OMV surface using both genetic engineering and "Plug-and-Display" technology. It showed that the bioengineered OMVs could elicit anti-tumor immune response decorated with different tumor antigens could elicit a synergistic antitumour immune response and abrogate lung melanoma metastasis. Utilizing the strong adjuvant effect of OMVs, Huang et al.[305] developed a nanovaccine by loading full-length fibroblast growth factor (BFGF) molecule onto bacterial OMVs *via* genetic engineering, which could effectively induce the host to produce persistent anti-BFGF autoantibodies after 3 immunizations to antagonize BFGF functions and achieve tumor regression. Besides genetic engineering, Irene et al.[306] exploited a novel engineering strategy to decorate OMVs with heterologous antigens by channeling them to the lipoprotein transport machinery, which was successfully validated with 5 *S. aureus* antigens, since lipidated antigens highly accumulated in the vesicular compartment.

OMVs could also employed as drug delivery vehicles due to their following advantages: (i) easily-acquired targeted abilities, since OMVs could decorated with targeting ligands by genetically engineering the parent bacteria; (ii) in favor of enhanced permeation and retention (EPR) effect owing to the size of OMVs; (iii) potential affinity to neutrophils and macrophages due to the presence of many different PAMPs; (iv) excellent immune-stimulation properties. For example, Guo et al.[307] reported a pH-sensitive bacterial OMVs platform to co-load PTX and Redd1-siRNA to regulate tumor metabolism microenvironment, which could be easily recognized and phagocytized by macrophages because of the immunogenic of OMVs, and finally achieve TAMs repolarization and tumor metastasis suppression. Additionally, Zhuang et al.[308] also fabricated a versatile bacterial OMVs-based nanoplatform by loading MerTK inhibitor UNC2025 into *E. coli MG1655*-derived OMVs, which synergized efferocytosis blockade by preventing the MerTK phosphorylation of TAMs with OMVs based immune augment to boost tumor-specific immunity.

Moreover, bacterial OMVs also possess the potential to be employed as cancer immunotherapy agents. For example, Kim et al.[309] prepared a kind of bacterial OMVs derived from genetically modified *E. coli*, where lipid component of LPS was moved to avoid possible adverse effects. The as-prepared bacterial OMVs could specifically accumulate in tumor tissue, and subsequently induce CXCL10 and IFN-γ production, thus resulting in long-term antitumor immune responses to eradicate established tumors. Although the universality of OMVs-induced antitumor activity has been widely reported, the applicability between OMV types and cancer types still deserves deep research due to diversity of OMVs and heterogeneity of tumors[16].

5. Conclusions and perspectives

In conclusion, we summarized the existing evidence supporting the existence of intratumoral microbiota across various types of cancers in this review, mainly focusing on the heterogeneity of intratumoral microbiota and the association of intratumoral microbiota composition with tumor prognostic events. Given the sophisticated and pluralistic relationships among host, microbiota composition and status of cancers, we further described the basic features of tumor microbe microenvironment, with an attempt to verify the potential mechanisms by which intratumoral microbiota exert specific anti-tumorigenic or pro-tumorigenic effects[11,310]. On one hand, intratumoral microbiota could enhance antitumor immunity *via* innate and adaptive immune activation, T and NK cell activation, tertiary lymphoid structure (TLS) production as well as intratumoral microbiota-derived antigen presenting; one the other hand, they could also decrease antitumor immune responses by T cell inactivation, ROS upregulation, and immunosuppression[15]. With the basic and clinical research in-depth, the mechanisms underlying intratumoral microbiota-promoted tumorigenesis have been gradually revealed, including DNA mutations, chronic inflammation, complement system, activating carcinogenic pathways and initiating metastasis, which involve in different signaling pathways such as TLR, ROS, β-catenin, STING, NF-κB and ERK[15]. These viewpoints may help identify the microbiota as diagnosis or prognosis evaluation of cancers, which provided valuable insight to develop multidisciplinary approach-based interventions of tumor microbiome for cancer therapy.

Given the various mechanisms underlying the interplay between tumor microbiome and cancer, intratumoral microbiota hold great therapeutic potentials to facilitate the development of tumor-specific treatments. Herein, we further explored the therapeutic potentials of intratumoral microbiota, and offered several novel anti-tumor strategies by applying wild-type or engineered live microbes, microbiota metabolites, antibiotics, synthetic biology, as well as rationally designed biomaterials to modulate tumor immunity *via* manipulating the composition and ecosystem of tumor microbe microenvironment. More specifically, the therapeutic approaches of intratumoral microbiota could include but not limit to the following: (i) serving as vectors, intratumoral microbiota could be employed to delivery anti-tumor agents or genes based on their intrinsic tumor-targeting

properties, furthermore, engineering microbiota vectors to express and produce cytotoxic drugs *in situ* is another effective way to strengthen antitumor effect, such as engineered nitric oxide-produced *H. pylori*[311]; (ii) targeted modulation of the microbiota components for cancer therapy, ablation of harmful microbiota (*i.e.*, use of antibiotics) and delivery of beneficial microbiota (*i.e.*, *Lactobacillus*) within the tumor have been approved efficient in clinical trials[211]; (iii) oncolytic viruses have exhibited charming results in antitumor therapies, which could induce cell lysis dependent on the sensitivity of tumor cells to viral infection, and reduce tumor by enhanced antigens presentation and blood vessels destroy, for example, T-VEC is an FDA-approved oncolytic virus for metastatic melanoma treatment[312]; (iv) intratumoral microbiota also possess great potential to be used as diagnostic and prognostic tools in addition to their therapeutic effects, it showed that intratumoral microbiome characteristics are widely related to the clinicopathological features of the tumor (*i.e.*, tumor stage and histological grade). Moreover, *H. pylori* in gastric cancer contributed to a higher disease risk and worse disease conditions, Proteobacteria was a major contributor to PDAC, and *F. nucleatum* was correlated with a higher risk of colorectal cancer[15]. Therefore, the rational use of intratumoral microbiota can serve as novel therapeutic strategy, diagnosis and prognosis evaluation for cancer therapy.

However, despite of these progresses, the researches around intratumoral microbes are still in their infancy, and many unanswered questions still need untangled: (i) the detection of intratumoral microbes is still challenging owing to low microbial biomass despite of rapid technological developments, which might lead to biased amplicon-based sequencing results, and lacked reproducibility due to limited clinical sample collection, additionally, how to avoid the samples being contaminated during the testing process, and how to eliminate the interference of environmental microbial contamination are another formidable task[2,10]; (ii) whether intratumoral microbiome play a direct causal role in tumorigenesis (cause or result) haven't been yet clearly established, although many intratumoral microbiome dysbiosis were found contribute to oncogenesis, and the sources of intratumoral microbiota remains perplexed, it isn't sure whether they originate from the local expansion of normal tissue-resident commensals or not[1,19]; (iii) as for the therapeutic application of intratumoral microbes, it keeps challenging to selectively manipulate the specific components of intratumoral microbes for targeted cancer therapy without affecting the gut microbiota or causing un-wanted dysbiosis, and the risk of safety issue can't be ignored, with urgent need for further animal testing and further clinical trial; (iv) although growing researches highlighted the roles of intratumoral microbes in cancer biology, the consistency of the results in different studies is poor, and contradictory conclusions were drew among these researches[2]. Therefore, it still has a long way to go, not only to address the above-mentioned challenges, but also to dig deeper about the underlying mechanisms.

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Author contributions

Ji Zheng, Jiayun Jiang and Chong Li proposed conception and edited manuscript; Yu Fu drafted and edited manuscript, figures and tables; Jia Li, Wenyun Cai, Yulan Huang, Xinlong Liu, Zhongyi Ma, Zhongjie Tang, and Xufei Bian participated drafting and editing manuscript as well as references. Yu Fu revised the manuscript. All of the authors have read and approved the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Liu JY, Zhang Y. Intratumor microbiome in cancer progression: current developments, challenges and future trends. *Biomark Res* 2022;**10**:1−18.
2. Xue C, Chu QF, Zheng QX, Yuan X, Su YS, Bao ZY, et al. Current understanding of the intratumoral microbiome in various tumors. *Cell Rep Med* 2023;**4**:100884.
3. Heymann CJF, Bard JM, Heymann MF, Heymann D, Bobin-Dubigeon C. The intratumoral microbiome: characterization methods and functional impact. *Cancer Lett* 2021;**522**:63−79.
4. Xie YF, Xie F, Zhou XX, Zhang L, Yang B, Huang J, et al. Microbiota in tumors: from understanding to application. *Adv Sci* 2022;**9**:e2200470.
5. Chen JW, Li T, Liang JH, Huang QQ, Huang JD, Ke YQ, et al. Current status of intratumour microbiome in cancer and engineered exogenous microbiota as a promising therapeutic strategy. *Biomed Pharmacother* 2022;**145**:112443.
6. Zhang N, Kandalai S, Zhou XZ, Hossain F, Zheng QF. Applying multi-omics toward tumor microbiome research. *iMeta* 2023;**2**:e73.
7. Wang Q, Liu ZQ, Ma AJ, Li ZH, Liu BQ, Ma Q. Computational methods and challenges in analyzing intratumoral microbiome data. *Trends Microbiol* 2023;**31**:707−22.
8. Zhang J, Du QQ, Song XW, Gao SS, Pang XC, Li Y, et al. Evaluation of the tumor-targeting efficiency and intratumor heterogeneity of anticancer drugs using quantitative mass spectrometry imaging. *Theranostics* 2020;**10**:2621−30.
9. Galeano Nino JL, Wu HR, 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.
10. Gong YY, Huang XQ, Wang MH, Liang XQ. Intratumor microbiota: a novel tumor component. *J Cancer Res Clin Oncol* 2023;**149**:6675−91.
11. Ma JY, Huang LJ, Hu D, Zeng S, Han Y, Shen H. The role of the tumor microbe microenvironment in the tumor immune microenvironment: bystander, activator, or inhibitor?. *J Exp Clin Cancer Res* 2021;**40**:327.
12. Zhou P, Hu YW, Wang XY, Shen LX, Liao XH, Zhu YJ, et al. Microbiome in cancer: an exploration of carcinogenesis, immune responses and immunotherapy. *Front Immunol* 2022;**13**:877939.
13. Zhou XZ, Kandalai S, Hossain F, Zheng QF. Tumor microbiome metabolism: a game changer in cancer development and therapy. *Front Oncol* 2022;**12**:933407.
14. Cogdill AP, Gaudreau PO, Arora R, Gopalakrishnan V, Wargo JA. The impact of intratumoral and gastrointestinal microbiota on systemic cancer therapy. *Trends Immunol* 2018;**39**:900−20.
15. Yang L, Li AT, Wang Y, Zhang Y. Intratumoral microbiota: roles in cancer initiation, development and therapeutic efficacy. *Signal Transduct Target Ther* 2023;**8**:1−24.

16. Li M, Zhou H, Yang C, Wu Y, Zhou XC, Liu H, et al. Bacterial outer membrane vesicles as a platform for biomedical applications: an update. *J Control Release* 2020;**323**:253−68.
17. Xue KK, Wang L, Liu JY. Bacterial outer membrane vesicles and their functionalization as vehicles for bioimaging, diagnosis and therapy. *Mater Adv* 2022;**3**:7185−97.
18. 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 Biot* 2020;**104**:2857−69.
19. 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.
20. Fu AK, Yao BQ, Dong TT, Chen YY, Yao J, Liu Y, et al. Tumor-resident intracellular microbiota promotes metastatic colonization in breast cancer. *Cell* 2022;**185**:1356−72.
21. Azevedo MM, Pina-Vaz C, Baltazar F. Microbes and cancer: friends or faux? *Int J Mol Sci* 2020;**21**:3115.
22. Bertocchi A, Carloni S, Ravenda PS, Bertalot G, Spadoni I, Lo Cascio A, et al. Gut vascular barrier impairment leads to intestinal bacteria dissemination and colorectal cancer metastasis to liver. *Cancer Cell* 2021;**39**:708−24.
23. Aykut B, Pushalkar S, Chen R, Li Q, Abengozar R, Kim JI, et al. The fungal mycobiome promotes pancreatic oncogenesis *via* activation of MBL. *Nature* 2019;**574**:264−7.
24. Banerjee S, Alwine JC, Wei Z, Tian T, Shih N, Sperling C, et al. Microbiome signatures in prostate cancer. *Carcinogenesis* 2019;**40**:749−64.
25. Huang S, Li JY, Wu J, Meng L, Shou CC. *Mycoplasma* infections and different human carcinomas. *World J Gastroenterol* 2001;**7**:266.
26. Pehlivan M, Itirli G, Onay H, Bulut H, Koyuncuoglu M, Pehlivan S. Does *Mycoplasma* sp. play role in small cell lung cancer?. *Lung Cancer* 2004;**45**:129−30.
27. Nakatsu G, Zhou HK, Wu WKK, Wong SH, Coker OO, Dai ZW, et al. Alterations in enteric virome are associated with colorectal cancer and survival outcomes. *Gastroenterology* 2018;**155**:529−41.
28. Agostinetto E, Gligorov J, Piccart M. Systemic therapy for early-stage breast cancer: learning from the past to build the future. *Nat Rev Clin Oncol* 2022;**19**:763−74.
29. Zheng C, Zhang W, Wang JM, Zhai YH, Xiong FQ, Cai Y, et al. Lenvatinib- and vadimezan-loaded synthetic high-density lipoprotein for combinational immunochemotherapy of metastatic triple-negative breast cancer. *Acta Pharm Sin B* 2022;**12**:3726−38.
30. Vitorino M, Costa DA, Vicente R, Caleca T, Santos C. Local breast microbiota: a "new" player on the block. *Cancers* 2022;**14**:3811.
31. Rao Malla R, Marni R, Kumari S, Chakraborty A, Lalitha P. Microbiome assisted tumor microenvironment: emerging target of breast cancer. *Clin Breast Cancer* 2022;**22**:200−11.
32. Xuan CY, Shamonki JM, Chung A, Dinome ML, Chung M, Sieling PA, et al. Microbial dysbiosis is associated with human breast cancer. *PLoS One* 2014;**9**:e83744.
33. Velicer CM, Heckbert SR, Lampe JW, Potter JD, Robertson CA, Taplin SH. Antibiotic use in relation to the risk of breast cancer. *JAMA* 2004;**291**:827−35.
34. Rossini A, Rumio C, Sfondrini L, Tagliabue E, Morelli D, Miceli R, et al. Influence of antibiotic treatment on breast carcinoma development in proto-neu transgenic mice. *Cancer Res* 2006;**66**:6219−24.
35. Urbaniak C, Gloor GB, Brackstone M, Scott L, Tangney M, Reid G. The microbiota of breast tissue and its association with breast cancer. *Appl Environ Microbiol* 2016;**82**:5039−48.
36. Urbaniak C, Cummins J, Brackstone M, Macklaim JM, Gloor GB, Baban CK, et al. Microbiota of human breast tissue. *Appl Environ Microbiol* 2014;**80**:3007−14.
37. Tzeng A, Sangwan N, Jia M, Liu CC, Keslar KS, Downs-Kelly E, et al. Human breast microbiome correlates with prognostic features and immunological signatures in breast cancer. *Genome Med* 2021;**13**:60.
38. Parhi L, Alon-Maimon T, Sol A, Nejman D, Shhadeh A, Fainsod-Levi T, et al. Breast cancer colonization by *Fusobacterium nucleatum* accelerates tumor growth and metastatic progression. *Nat Commun* 2020;**11**:3259.
39. Erb-Downward JR, Thompson DL, Han MK, Freeman CM, McCloskey L, Schmidt LA, et al. Analysis of the lung microbiome in the "healthy" smoker and in COPD. *PLoS One* 2011;**6**:e16384.
40. Ramirez-Labrada AG, Isla D, Artal A, Arias M, Rezusta A, Pardo J, et al. The influence of lung microbiota on lung carcinogenesis, immunity, and immunotherapy. *Trends Cancer* 2020;**6**:86−97.
41. Yu GQ, 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.
42. Sommariva M, Le Noci V, Bianchi F, Camelliti S, Balsari A, Tagliabue E, et al. The lung microbiota: role in maintaining pulmonary immune homeostasis and its implications in cancer development and therapy. *Cell Mol Life Sci* 2020;**77**:2739−49.
43. Dickson RP, Erb-Downward JR, Martinez FJ, Huffnagle GB. The microbiome and the respiratory tract. *Annu Rev Physiol* 2016;**78**:481−504.
44. Mathieu E, Escribano-Vazquez U, Descamps D, Cherbuy C, Langella P, Riffault S, et al. Paradigms of lung microbiota functions in health and disease. *Front Physiol* 2018;**9**:1168.
45. Liu NN, Yi CX, Wei LQ, Zhou JA, Jiang T, Hu CC, et al. The intratumor mycobiome promotes lung cancer progression via myeloid-derived suppressor cells. *Cancer Cell* 2023;**41**:1−18.
46. Palucka AK, Coussens LM. The basis of oncoimmunology. *Cell* 2016;**164**:1233−47.
47. Dumont-Leblond N, Veillette M, Racine C, Joubert P, Duchaine C. Non-small cell lung cancer microbiota characterization: prevalence of enteric and potentially pathogenic bacteria in cancer tissues. *PLoS One* 2021;**16**:e0249832.
48. Cheng C, Wang ZF, Wang JQ, Ding C, Sun C, Liu PL, et al. Characterization of the lung microbiome and exploration of potential bacterial biomarkers for lung cancer. *Trans Lung Cancer Res* 2020;**9**:693−704.
49. Zhang M, Zhang Y, Sun Y, Wang S, Liang H, Han YG. 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.
50. Najafi S, Abedini F, Jamalkandi SA, Shariati P, Ahmadi A, Fesharaki MG. The composition of lung microbiome in lung cancer: a systematic review and meta-analysis. *BMC Microbiol* 2021;**21**:315.
51. Zhao YM, Yi JQ, Xiang JJ, Jia W, Chen AQ, Chen LY, et al. Exploration of lung mycobiome in the patients with non-small-cell lung cancer. *BMC Microbiol* 2023;**23**:81.
52. Lloyd CM, Marsland BJ. Lung homeostasis: influence of age, microbes, and the immune system. *Immunity* 2017;**46**:549−61.
53. Jin CC, Lagoudas GK, Zhao C, Bullman S, Bhutkar A, Hu B, et al. Commensal microbiota promote lung cancer development *via* gammadelta T cells. *Cell* 2019;**176**:998−1013.
54. Peters BA, Hayes RB, Goparaju C, Reid C, Pass HI, Ahn JY. The microbiome in lung cancer tissue and recurrence-free survival. *Cancer Epidemiol Biomarkers Prev* 2019;**28**:731−40.
55. Gollwitzer ES, Saglani S, Trompette A, Yadava K, Sherburn R, McCoy KD, et al. Lung microbiota promotes tolerance to allergens in neonates *via* PD-L1. *Nat Med* 2014;**20**:642−7.
56. Hwang WL, Jagadeesh KA, Guo JA, Hoffman HI, Yadollahpour P, Reeves JW, et al. Single-nucleus and spatial transcriptome profiling of pancreatic cancer identifies multicellular dynamics associated with neoadjuvant treatment. *Nat Genet* 2022;**54**:1178−91.
57. Springfeld C, Ferrone CR, Katz MHG, Philip PA, Hong TS, Hackert T, et al. Neoadjuvant therapy for pancreatic cancer. *Nat Rev Clin Oncol* 2023;**20**:318−37.
58. Kiaie SH, Sanaei MJ, Heshmati M, Asadzadeh Z, Azimi I, Hadidi S, et al. Immune checkpoints in targeted-immunotherapy of pancreatic cancer: new hope for clinical development. *Acta Pharm Sin B* 2021;**11**:1083−97.

59. Wei MY, Shi S, Liang C, Meng QC, Hua J, Zhang YY, et al. The microbiota and microbiome in pancreatic cancer: more influential than expected. *Mol Cancer* 2019;**18**:97.
60. Leinwand J, Miller G. Regulation and modulation of antitumor immunity in pancreatic cancer. *Nat Immunol* 2020;**21**:1152−9.
61. Arsenijevic T, Nicolle R, Bouchart C, D'Haene N, Demetter P, Puleo F, et al. Pancreatic cancer meets human microbiota: close encounters of the third kind. *Cancers* 2021;**13**:1231.
62. Cohen JR, Shannon AB, McNEAL JE, Shannon T, Garrett LK. *Propionibacterium acnes* associated with inflammation in radical prostatectomy specimens: a possible link to cancer evolution?. *J Urology* 2005;**173**:1969−74.
63. McAllister F, Khan MAW, Helmink B, Wargo JA. The tumor microbiome in pancreatic cancer: bacteria and beyond. *Cancer Cell* 2019;**36**:577−9.
64. 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.
65. Capula M, Peran M, Xu G, Donati V, Yee D, Gregori A, et al. Role of drug catabolism, modulation of oncogenic signaling and tumor microenvironment in microbe-mediated pancreatic cancer chemoresistance. *Drug Resist Updat* 2022;**64**:100864.
66. Guo W, Zhang YC, Guo SW, Mei Z, Liao HP, Dong H, et al. Tumor microbiome contributes to an aggressive phenotype in the basal-like subtype of pancreatic cancer. *Commun Biol* 2021;**4**:1019.
67. Driscoll JA, Brody SL, Kollef MH. The epidemiology, pathogenesis and treatment of *Pseudomonas aeruginosa* infections. *Drugs* 2007;**67**:351−68.
68. Riquelme E, Zhang Y, Zhang LL, Montiel M, Zoltan M, Dong WL, et al. Tumor microbiome diversity and composition influence pancreatic cancer outcomes. *Cell* 2019;**178**:795−806.
69. Sun DD, Zou YF, Song L, Han SL, Yang H, Chu D, et al. A cyclodextrin-based nanoformulation achieves co-delivery of ginsenoside Rg3 and quercetin for chemo-immunotherapy in colorectal cancer. *Acta Pharm Sin B* 2022;**12**:378−93.
70. Wong SH, Yu J. Gut microbiota in colorectal cancer: mechanisms of action and clinical applications. *Nat Rev Gastroenterol Hepatol* 2019;**16**:690−704.
71. Dejea CM, Fathi P, Craig JM, Boleij A, Taddese R, Geis AL, et al. Patients with familial adenomatous polyposis harbor colonic biofilms containing tumorigenic bacteria. *Science* 2018;**359**:592−7.
72. Wu SG, Rhee KJ, Albesiano E, Rabizadeh S, Wu XQ, Yen HR, et al. A human colonic commensal promotes colon tumorigenesis *via* activation of T helper type 17 T cell responses. *Nat Med* 2009;**15**:1016−22.
73. Arthur JC, Perez-Chanona E, Mühlbauer M, Tomkovich S, Uronis JM, Fan TJ, et al. Intestinal inflammation targets cancer-inducing activity of the microbiota. *Science* 2012;**338**:120−3.
74. Flemer B, Lynch DB, Brown JM, Jeffery IB, Ryan FJ, Claesson MJ, et al. Tumour-associated and non-tumour-associated microbiota in colorectal cancer. *Gut* 2017;**66**:633−43.
75. Castellarin M, Warren RL, Freeman JD, Dreolini L, Krzywinski M, Strauss J, et al. *Fusobacterium nucleatum* infection is prevalent in human colorectal carcinoma. *Genome Res* 2012;**22**:299−306.
76. Kostic AD, Gevers D, Pedamallu CS, Michaud M, Duke F, Earl AM, et al. Genomic analysis identifies association of *Fusobacterium* with colorectal carcinoma. *Genome Res* 2012;**22**:292−8.
77. Abed J, Emgard JE, Zamir G, Faroja M, Almogy G, Grenov A, et al. Fap2 mediates *Fusobacterium nucleatum* colorectal adenocarcinoma enrichment by binding to tumor-expressed Gal-GalNAc. *Cell Host Microbe* 2016;**20**:215−25.
78. Bullman S, Pedamallu CS, Sicinska E, Clancy TE, Zhang X, Cai DN, et al. Analysis of *Fusobacterium* persistence and antibiotic response in colorectal cancer. *Science* 2017;**358**:1443−8.
79. LaCourse KD, Johnston CD, Bullman S. The relationship between gastrointestinal cancers and the microbiota. *Lancet Gastroenterol Hepatol* 2021;**6**:498−509.
80. Peek Jr RM, Crabtree JE. *Helicobacter* infection and gastric neoplasia. *J Pathol* 2006;**208**:233−48.
81. Aviles-Jimenez F, Vazquez-Jimenez F, Medrano-Guzman R, Mantilla A, Torres J. Stomach microbiota composition varies between patients with non-atrophic gastritis and patients with intestinal type of gastric cancer. *Sci Rep* 2014;**4**:4202.
82. Dicksved J, Lindberg M, Rosenquist M, Enroth H, Jansson JK, Engstrand L. Molecular characterization of the stomach microbiota in patients with gastric cancer and in controls. *J Med Microbiol* 2009;**58**:509−16.
83. Eun CS, Kim BK, Han DS, Kim SY, Kim KM. Choi BY, et al. Differences in gastric mucosal microbiota profiling in patients with chronic gastritis, intestinal metaplasia, and gastric cancer using pyrosequencing methods. *Helicobacter* 2014;**19**:407−16.
84. Coker OO, Dai ZW, Nie YZ, Zhao GJ, Cao L, Nakatsu G, et al. Mucosal microbiome dysbiosis in gastric carcinogenesis. *Gut* 2018;**67**:1024−32.
85. Park CH, Lee JG, Lee AR, Eun CS, Han DS. Network construction of gastric microbiome and organization of microbial modules associated with gastric carcinogenesis. *Sci Rep* 2019;**9**:12444.
86. Ai B, Mei Y, Liang D, Wang TJ, 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.
87. Park JY, Seo H, Kang CS, Shin TS, Kim JW, Park JM, et al. Dysbiotic change in gastric microbiome and its functional implication in gastric carcinogenesis. *Sci Rep* 2022;**12**:4285.
88. Bast RC, Hennessy B, Mills GB. The biology of ovarian cancer: new opportunities for translation. *Nat Rev Cancer* 2009;**9**:415−28.
89. Chang LL, Hu Y, Fu YY, Zhou TY, You J, Du JM, et al. Targeting slug-mediated non-canonical activation of c-Met to overcome chemo-resistance in metastatic ovarian cancer cells. *Acta Pharm Sin B* 2019;**9**:484−95.
90. Carvalho JP, Carvalho FM. Is *Chlamydia*-infected tubal fimbria the origin of ovarian cancer? *Med Hypotheses* 2008;**71**:690−3.
91. Hosseininasab-nodoushan SA, Ghazvini K, Jamialahmadi T, Keikha M, Sahebkar A. Association of *Chlamydia* and *Mycoplasma* infections with susceptibility to ovarian cancer: a systematic review and meta-analysis. *Semin Cancer Biol* 2022;**86**:923−8.
92. Sipos A, Ujlaki G, Mikó E, Maka E, Szabó J, Uray K, et al. The role of the microbiome in ovarian cancer: mechanistic insights into oncobiosis and to bacterial metabolite signaling. *Mol Med* 2021;**27**:33.
93. Miles SM, Hardy BL, Merrell DS. Investigation of the microbiota of the reproductive tract in women undergoing a total hysterectomy and bilateral salpingo-oopherectomy. *Fertil Steril* 2017;**107**:813−20.
94. Banerjee S, Tian T, Wei Z, Shih N, Feldman MD, Alwine JC, et al. The ovarian cancer oncobiome. *Oncotarget* 2017;**8**:36225.
95. Kumar P, Ranmale S, Tongaonkar H, Mehta S, Mania-Pramanik J. Human papillomavirus infection: is it associated with epithelial ovarian cancer? *Indian J Med Microbi* 2021;**39**:311−4.
96. Al-Shabanah OA, Hafez MM, Hassan ZK, Sayed-Ahmed MM, Abozeed WN, Al-Rejaie SS, et al. Human papillomavirus genotyping and integration in ovarian cancer Saudi patients. *Virol J* 2013;**10**:343.
97. Zhou B, Sun CY, Huang J, Xia M, Guo ES, Li N, et al. The biodiversity composition of microbiome in ovarian carcinoma patients. *Sci Rep* 2019;**9**:1691.
98. Omar MI, MacLennan S, Ribal MJ, Roobol MJ, Dimitropoulos K, van den Broeck T, et al. Unanswered questions in prostate cancer—findings of an international multi-stakeholder consensus by the PIONEER consortium. *Nat Rev Urol* 2023;**20**:494−501.
99. Liadi Y, Campbell T, Dike P, Harlemon M, Elliott B, Odero-Marah V. Prostate cancer metastasis and health disparities: a systematic review. *Prostate Cancer P D* 2023;**1**:1−9.
100. 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.
101. Sfanos KS, De Marzo AM. Prostate cancer and inflammation: the evidence. *Histopathology* 2012;**60**:199−215.

102. Kwon OJ, Zhang L, Ittmann MM, Xin L. Prostatic inflammation enhances basal-to-luminal differentiation and accelerates initiation of prostate cancer with a basal cell origin. *Proc Natl Acad Sci U S A* 2014;**111**:592−600.
103. Simons BW, Durham NM, Bruno TC, Grosso JF, Schaeffer AJ, Ross AE, et al. A human prostatic bacterial isolate alters the prostatic microenvironment and accelerates prostate cancer progression. *J Pathol* 2015;**235**:478−89.
104. Davidsson S, Mölling P, Rider JR, Unemo M, Karlsson MG, Carlsson J, et al. Frequency and typing of *Propionibacterium acnes* in prostate tissue obtained from men with and without prostate cancer. *Infect Agents Cancer* 2016;**11**:26.
105. McDowell A, Valanne S, Ramage G, Tunney MM, Glenn JV, McLorinan GC, et al. *Propionibacterium acnes* types I and II represent phylogenetically distinct groups. *J Clin Microbiol* 2005;**43**:326−34.
106. Drott JB, Alexeyev O, Bergström P, Elgh F, Olsson J. *Propionibacterium acnes* infection induces upregulation of inflammatory genes and cytokine secretion in prostate epithelial cells. *BMC Microbiol* 2010;**10**:126.
107. Fehri LF, 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.
108. Bielecki R, Zdrodowska-Stefanow B, Ostaszewska-Puchalska I, Baltaziak M, Kozłowski BM. Subclinical prostatic inflammation attributable to *Chlamydia trachomatis* in a patient with prostate cancer. *Med Wieku Rozwoj* 2005;**9**:87−91.
109. Cavarretta I, Ferrarese R, Cazzaniga W, Saita D, Luciano R, Ceresola ER, et al. The microbiome of the prostate tumor microenvironment. *Eur Urol* 2017;**72**:625−31.
110. Feng Y, Ramnarine VR, Bell R, Volik S, Davicioni E, Hayes VM, et al. Metagenomic and metatranscriptomic analysis of human prostate microbiota from patients with prostate cancer. *BMC Genom* 2019;**20**:146.
111. Grice EA, Kong HH, Conlan S, Deming CB, Davis J, Young AC, et al. Topographical and temporal diversity of the human skin microbiome. *Science* 2009;**324**:1190−2.
112. 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.
113. Sepich-Poore GD, Carter H, Knight R. Intratumoral bacteria generate a new class of therapeutically relevant tumor antigens in melanoma. *Cancer Cell* 2021;**39**:601−3.
114. Davar D, Dzutsev AK, McCulloch JA, Rodrigues RR, Chauvin JM, Morrison RM, et al. Fecal microbiota transplant overcomes resistance to anti−PD-1 therapy in melanoma patients. *Science* 2021;**371**:595−602.
115. Zhu GJ, Su HX, Johnson CH, Khan SA, Kluger H, Lu LG. Intratumour microbiome associated with the infiltration of cytotoxic CD8+ T cells and patient survival in cutaneous melanoma. *Eur J Cancer* 2021;**151**:25−34.
116. Nakatsuji T, Chen TH, Butcher AM, Trzoss LL, Nam SJ, Shirakawa KT, et al. A commensal strain of *Staphylococcus epidermidis* protects against skin neoplasia. *Sci Adv* 2018;**4**:eaao4502.
117. Du DY, Liu C, Qin MY, Zhang X, Xi T, Yuan ST, et al. Metabolic dysregulation and emerging therapeutical targets for hepatocellular carcinoma. *Acta Pharm Sin B* 2022;**12**:558−80.
118. Yuan JM, Govindarajan S, Arakawa K, Yu MC. Synergism of alcohol, diabetes, and viral hepatitis on the risk of hepatocellular carcinoma in blacks and whites in the U.S. *Cancer* 2004;**101**:1009−17.
119. Chakladar J, Wong LM, Kuo SZ, Li WT, Yu MA, Chang EY, et al. The liver microbiome is implicated in cancer prognosis and modulated by alcohol and hepatitis B. *Cancers* 2020;**12**:1642.
120. Qu DD, Wang Y, Xia QX, Chang J, Jiang XN, Zhang H. Intratumoral microbiome of human primary liver cancer. *Hepatol Commun* 2022;**6**:1741−52.
121. Liao JF, Han RX, Wu YZ, Qian ZY. Review of a new bone tumor therapy strategy based on bifunctional biomaterials. *Bone Res* 2021;**9**:18.
122. Nakagawa M, SuGIURA Y, OsHIMA T, Kajino G, Hirako H, Yamada Y. Urinary hydroxyproline excretion in orthopedic disease, with special reference to systemic bone disease and bone tumor (secondary report). *Nagoya J Med Sci* 1967;**29**:345−67.
123. Huang Y, Fan XG, Wang ZM, Zhou JH, Tian XF, Li N. Identification of helicobacter species in human liver samples from patients with primary hepatocellular carcinoma. *J Clin Pathol* 2004;**57**:1273−7.
124. Klann E, Williamson JM, Tagliamonte MS, Ukhanova M, Asirvatham JR, Chim H, et al. Microbiota composition in bilateral healthy breast tissue and breast tumors. *Cancer Causes Control* 2020;**31**:1027−38.
125. Thompson KJ, Ingle JN, Tang XJ, Chia N, Jeraldo PR, Walther-Antonio MR, et al. A comprehensive analysis of breast cancer microbiota and host gene expression. *PLoS One* 2017;**12**:e0188873.
126. 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.
127. Wong LM, Shende N, Li WT, Castaneda G, Apostol L, Chang EY, et al. Comparative analysis of age- and gender-associated microbiome in lung adenocarcinoma and lung squamous cell carcinoma. *Cancers* 2020;**12**:1447.
128. Lee SH, Sung JY, Yong D, Chun J, Kim SY, Song JH, et al. Characterization of microbiome in bronchoalveolar lavage fluid of patients with lung cancer comparing with benign mass like lesions. *Lung Cancer* 2016;**102**:89−95.
129. Tsay JCJ, Wu BG, Sulaiman I, Gershner K, Schluger R, Li YH, et al. Lower airway dysbiosis affects lung cancer progression. *Cancer Discov* 2021;**11**:293−307.
130. Greathouse KL, White JR, Vargas AJ, Bliskovsky VV, Beck JA, Muhlinen NV, et al. Interaction between the microbiome and TP53 in human lung cancer. *Genome Biol* 2018;**19**:123.
131. Tsay JCJ, Wu BG, Badri MH, Clemente JC, Shen N, Meyn P, et al. Airway microbiota is associated with upregulation of the PI3K pathway in lung cancer. *Am J Respir Crit Care Med* 2018;**198**:1188−98.
132. Burns MB, Lynch J, Starr TK, Knights D, Blekhman R. Virulence genes are a signature of the microbiome in the colorectal tumor microenvironment. *Genome Med* 2015;**7**:55.
133. 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.
134. Kosumi K, Hamada T, Koh H, Borowsky J, Bullman S, Twombly TS, et al. The amount of *Bifidobacterium* genus in colorectal carcinoma tissue in relation to tumor characteristics and clinical outcome. *Am J Pathol* 2018;**188**:2839−52.
135. Liu WX, Zhang X, Xu HZ, Li SM, Lau HCH, Chen QY, et al. Microbial community heterogeneity within colorectal neoplasia and its correlation with colorectal carcinogenesis. *Gastroenterology* 2021;**160**:2395−408.
136. Yu GQ, Torres J, Hu N, Medrano-Guzman R, Herrera-Goepfert R, Humphrys MS, et al. Molecular characterization of the human stomach microbiota in gastric cancer patients. *Front Cell Infect Microbiol* 2017;**7**:302.
137. Shao DT, Vogtmann E, Liu AQ, Qin JJ, 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.
138. Mrazek J, Mekadim C, Kucerova P, Svejstil R, Salmonova H, Vlasakova J, et al. Melanoma-related changes in skin microbiome. *Folia Microbiol* 2019;**64**:435−42.
139. Al-Shabanah OA, Hafez MM, Hassan ZK, Sayed-Ahmed MM, Abozeed WN, Al-Rejaie SS, et al. Human papillomavirus genotyping and integration in ovarian cancer Saudi patients. *Virol J* 2013;**10**:1−9.

140. Ma JY, 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* 2020;**12**:2524.
141. Chakladar J, Kuo SZ, Castaneda G, Li WT, Gnanasekar A, Yu MA, et al. The pancreatic microbiome is associated with carcinogenesis and corse prognosis in males and smokers. *Cancers* 2020;**12**:2672.
142. Gaiser RA, Halimi A, Alkharaan H, Lu LY, Davanian H, Healy K, et al. Enrichment of oral microbiota in early cystic precursors to invasive pancreatic cancer. *Gut* 2019;**68**:2186−94.
143. Li S, Fuhler GM, Bn N, Jose T, Bruno MJ, Peppelenbosch MP, et al. Pancreatic cyst fluid harbors a unique microbiome. *Microbiome* 2017;**5**:147.
144. Nalluri H, Jensen E, Staley C. Role of biliary stent and neoadjuvant chemotherapy in the pancreatic tumor microbiome. *BMC Microbiol* 2021;**21**:280.
145. Pushalkar S, Hundeyin M, Daley D, Zambirinis CP, Kurz E, Mishra A, et al. The pancreatic cancer microbiome promotes oncogenesis by induction of innate and adaptive immune suppression. *Cancer Discov* 2018;**8**:403−16.
146. 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.
147. 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.
148. Hooper SJ, Crean SJ, Lewis MA, Spratt DA, Wade WG, Wilson MJ. Viable bacteria present within oral squamous cell carcinoma tissue. *J Clin Microbiol* 2006;**44**:1719−25.
149. Liu Y, Baba Y, Ishimoto T, Tsutsuki H, Zhang TL, Nomoto D, et al. *Fusobacterium nucleatum* confers chemoresistance by modulating autophagy in oesophageal squamous cell carcinoma. *Br J Cancer* 2021;**124**:963−74.
150. Kaakoush NO, Castano-Rodriguez N, Man SM, Mitchell HM. Is *Campylobacter* to esophageal adenocarcinoma as *Helicobacter* is to gastric adenocarcinoma?. *Trends Microbiol* 2015;**23**:455−62.
151. 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.
152. Garrett WS. Cancer and the microbiota. *Science* 2015;**348**:80−6.
153. Andreeva NV, Gabbasova RR, Grivennikov SI. Microbiome in cancer progression and therapy. *Curr Opin Microbiol* 2020;**56**:118−26.
154. Peng MF, Tabashsum Z, Patel P, Bernhardt C, Biswas D. Linoleic acids overproducing *Lactobacillus casei* limits growth, survival, and virulence of *Salmonella Typhimurium* and enterohaemorrhagic *Escherichia coli*. *Front Microbiol* 2018;**9**:2663.
155. Litvak Y, Mon KKZ, Nguyen H, Chanthavixay G, Liou M, Velazquez EM, et al. Commensal *Enterobacteriaceae* protect against *Salmonella* colonization through oxygen competition. *Cell Host Microbe* 2019;**25**:128−39.
156. Nauts HC, Fowler GA, BogatkoFH. A review of the influence of bacterial infection and of bacterial products (Coley's toxins) on malignant tumors in man, a critical analysis of 30 inoperable cases treated by Coley's mixed toxins, in which diagnosis was confirmed by microscopic examination selected for special study. *Acta Med Scand Suppl* 1953;**276**:1−103.
157. Cheng M, Qian LT, Shen GD, Bian G, Xu TJ, Xu WP, et al. Microbiota modulate tumoral immune surveillance in lung through a δT17 immune cell-dependent mechanism. *Cancer Res* 2014;**74**:4030−41.
158. Marinelli L, Tenore GC, Novellino E. Probiotic species in the modulation of the anticancer immune response. *Semin Cancer Biol* 2017;**46**:182−90.
159. Furusawa Y, Obata Y, Fukuda S, Endo TA, Nakato G, Takahashi D, et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature* 2013;**504**:446−50.
160. Galluzzi L, Vitale I, Senovilla L, Olaussen KA, Pinna G, Eisenberg T, et al. Prognostic impact of vitamin B6 metabolism in lung cancer. *Cell Rep* 2012;**2**:257−69.
161. Iida N, Dzutsev A, Stewart CA, Smith L, Bouladoux N, Weingarten RA, et al. Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. *Science* 2013;**342**:967−70.
162. Vétizou M, Pitt JM, Daillère R, Lepage P, Waldschmitt N, Flament C, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. *Science* 2015;**350**:1079−84.
163. Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, Karpinets TV, et al. Gut microbiome modulates response to anti−PD-1 immunotherapy in melanoma patients. *Science* 2018;**359**:97−103.
164. Gonzalez-Sanchez P, DeNicola GM. The microbiome(s) and cancer: know thy neighbor(s). *J Pathol* 2021;**254**:332−43.
165. Kostic AD, Chun EY, Robertson L, Glickman JN, Gallini CA, Michaud M, et al. *Fusobacterium nucleatum* potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. *Cell Host Microbe* 2013;**14**:207−15.
166. Grivennikov SI, Wang KP, 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.
167. Dinges MM, Orwin PM, Schlievert PM. Exotoxins of *Staphylococcus aureus*. *Clin Microbiol Rev* 2000;**13**:16−34.
168. Rossi T, Vergara D, Fanini F, Maffia M, Bravaccini S, Pirini F. Microbiota-derived metabolites in tumor progression and metastasis. *Int J Mol Sci* 2020;**21**:5786.
169. Akira S, Hemmi H. Recognition of pathogen-associated molecular patterns by TLR family. *Immunol Lett* 2003;**85**:85−95.
170. Escamilla-Tilch M, Filio-Rodriguez G, Garcia-Rocha R, Mancilla-Herrera I, Mitchison NA, Ruiz-Pacheco JA, et al. The interplay between pathogen-associated and danger-associated molecular patterns: an inflammatory code in cancer? *Immunol Cell Biol* 2013;**91**:601−10.
171. Demento SL, Siefert AL, Bandyopadhyay A, Sharp FA, Fahmy TM. Pathogen-associated molecular patterns on biomaterials: a paradigm for engineering new vaccines. *Trends Biotechnol* 2011;**29**:294−306.
172. Guo JM, De May H, Franco S, Noureddine A, Tang L, Brinker CJ, et al. Cancer vaccines from cryogenically silicified tumour cells functionalized with pathogen-associated molecular patterns. *Nat Biomed Eng* 2022;**6**:19−31.
173. Zelechowska P, Brzezinska-Blaszczyk E, Agier J, Kozlowska E. Different effectiveness of fungal pathogen-associated molecular patterns (PAMPs) in activating rat peritoneal mast cells. *Immunol Lett* 2022;**248**:7−15.
174. Keller NP. Fungal secondary metabolism: regulation, function and drug discovery. *Nat Rev Microbiol* 2019;**17**:167−80.
175. Patel S, Seshadri S, Dalai S. Chapter seven-gut microbiome and type 2 diabetes. In: Das B, Singh V, editors. *Progress in molecular biology and translational science*, **191**. Amsterdam: Elsevier; 2022. p. 175−85.
176. Tan J, McKenzie C, Potamitis M, Thorburn AN, Mackay CR, Macia L. The role of short-chain fatty acids in health and disease. *Adv Immunol* 2014;**121**:91−119.
177. Silva YP, Bernardi A, Frozza RL. The role of short-chain fatty acids from gut microbiota in gut-brain communication. *Front Endocrinol* 2020;**11**:1−14.
178. Hee BVD, Wells JM. Microbial regulation of host physiology by short-chain fatty acids. *Trends Microbiol* 2021;**29**:700−12.
179. Guan BY, Tong JL, Hao HP, Yang ZX, Chen KJ, Xu H, et al. Bile acid coordinates microbiota homeostasis and systemic immunometabolism in cardiometabolic diseases. *Acta Pharm Sin B* 2022;**12**:2129−49.
180. Cook JW, Kennaway EL, Kennaway NM. Production of tumours in mice by deoxycholic acid. *Nature* 1940;**145**:627.
181. Crowley-Weber CL, Payne CM, Gleason-Guzman M, Watts GS, Futscher B, Waltmire CN, et al. Development and molecular

characterization of HCT-116 cell lines resistant to the tumor promoter and multiple stress-inducer, deoxycholate. *Carcinogenesis* 2002;**23**:2063−80.
182. Powolny A, Xu J, Loo G. Deoxycholate induces DNA damage and apoptosis in human colon epithelial cells expressing either mutant or wild-type p53. *Int J Biochem Cell B* 2001;**33**:193−203.
183. Khan AU, Mei YH, Wilson T. A proposed function for spermine and spermidine: protection of replicating DNA against damage by singlet oxygen. *Proc Natl Acad Sci U S A* 1992;**89**:11426−7.
184. Smith RC, Litwin MS, Lu Y, Zetter BR. Identification of an endogenous inhibitor of prostatic carcinoma cell growth. *Nat Med* 1995;**1**:1040−5.
185. Wang XJ, Feith DJ, Welsh P, Coleman CS, Lopez C, Woster PM, et al. Studies of the mechanism by which increased spermidine/spermine N1-acetyltransferase activity increases susceptibility to skin carcinogenesis. *Carcinogenesis* 2007;**28**:2404−11.
186. Richarme G, Liu C, Mihoub M, Abdallah J, Leger T, Joly N, et al. Guanine glycation repair by DJ-1/Park7 and its bacterial homologs. *Science* 2017;**357**:208−11.
187. Richarme G, Mihoub M, Dairou J, Bui LC, Leger T, Lamouri A. Parkinsonism-associated protein DJ-1/Park7 is a major protein deglycase that repairs methylglyoxal- and glyoxal-glycated cysteine, arginine, and lysine residues. *J Biol Chem* 2015;**290**:1885−97.
188. Bollong MJ, Lee G, Coukos JS, Yun H, Zambaldo C, Chang JW, et al. A metabolite-derived protein modification integrates glycolysis with KEAP1−NRF2 signalling. *Nature* 2018;**562**:600−4.
189. Cuevas-Ramos G, Petit CR, Marcq I, Boury M, Oswald E, Nougayrède JP. *Escherichia coli* induces DNA damage *in vivo* and triggers genomic instability in mammalian cells. *Proc Natl Acad Sci U S A* 2010;**107**:11537−42.
190. Nougayrède JP, Homburg S, Taieb F, Boury M, Brzuszkiewicz E, Gottschalk G, et al. *Escherichia coli* induces DNA double-strand breaks in eukaryotic cells. *Science* 2006;**313**:848−51.
191. Guo CJ, Chang FY, Wyche TP, Backus KM, Acker TM, Funabashi M, et al. Discovery of reactive microbiota-derived metabolites that inhibit host proteases. *Cell* 2017;**168**:517−26.
192. Zheng QF, Wang QL, Wang SF, Wu JQ, Gao Q, Liu W. Thiopeptide antibiotics exhibit a dual mode of action against intracellular pathogens by affecting both host and microbe. *Chem Biol* 2015;**22**:1002−7.
193. Vinogradov AA, Suga H. Introduction to thiopeptides: biological activity, biosynthesis, and strategies for functional reprogramming. *Cell Chem Biol* 2020;**27**:1032−51.
194. Xiang HG, Zhou M, Li Y, Zhou L, Wang RX. Drug discovery by targeting the protein−protein interactions involved in autophagy. *Acta Pharm Sin B* 2023;**13**:4373−90.
195. Hu W, Chan H, Lu L, Wong KT, Wong SH, Li MX, et al. Autophagy in intracellular bacterial infection. *Semin Cell Dev Biol* 2020;**101**:41−50.
196. Huang J, Brumell JH. Bacteria-autophagy interplay: a battle for survival. *Nat Rev Microbiol* 2014;**12**:101−14.
197. Deretic V, Delgado M, Vergne I, Master S, Haro SD, Ponpuak M, et al. Autophagy in immunity against *Mycobacterium* tuberculosis: a model system to dissect immunological roles of autophagy. In: Levine B, Yoshimori T, Deretic V, editors. *Autophagy in Infection and Immunity*. Berlin: Springer Berlin Heidelberg; 2009. p. 169−88.
198. Amano A, Nakagawa I, Yoshimori T. Autophagy in innate immunity against intracellular bacteria. *J Biochem* 2006;**140**:161−6.
199. Siqueira MDS, Ribeiro RM, Travassos LH. Autophagy and its interaction with intracellular bacterial pathogens. *Front Immunol* 2018;**9**:935.
200. Singh SB, Davis AS, Taylor GA, Deretic V. Human IRGM induces autophagy to eliminate intracellular *Mycobacteria*. *Science* 2006;**313**:1438−41.
201. Ogawa M, Yoshimori T, Suzuki T, Sagara H, Mizushima N, Sasakawa C. Escape of intracellular *Shigella* from autophagy. *Science* 2005;**307**:727−31.
202. Py BF, Lipinski MM, Yuan J. Autophagy limits *Listeria* monocytogenes intracellular growth in the early phase of primary infection. *Autophagy* 2007;**3**:117−25.
203. Chavez-Dominguez R, Perez-Medina M, Lopez-Gonzalez JS, Galicia-Velasco M, Aguilar-Cazares D. The double-edge sword of autophagy in cancer: from tumor suppression to pro-tumor activity. *Front Oncol* 2020;**10**:578418.
204. Ferraresi A, Girone C, Esposito A, Vidoni C, Vallino L, Secomandi E, et al. How autophagy shapes the tumor microenvironment in ovarian cancer. *Front Oncol* 2020;**10**:599915.
205. Mukhopadhyay S, Mahapatra KK, Praharaj PP, Patil S, Bhutia SK. Recent progress of autophagy signaling in tumor microenvironment and its targeting for possible cancer therapeutics. *Semin Cancer Biol* 2022;**85**:196−208.
206. Greten FR, Grivennikov SI. Inflammation and cancer: triggers, mechanisms, and consequences. *Immunity* 2019;**51**:27−41.
207. Chen J, Pitmon E, Microbiome Wang K. Inflammation and colorectal cancer. *Semin Immunol* 2017;**32**:43−53.
208. Goodman B, Gardner H. The microbiome and cancer. *J Pathol* 2018;**244**:667−76.
209. Gagliani N, Hu B, Huber S, Elinav E, Flavell RA. The fire within: microbes inflame tumors. *Cell* 2014;**157**:776−83.
210. Arthur JC, Jobin C. The complex interplay between inflammation, the microbiota and colorectal cancer. *Gut Microb* 2013;**4**:253−8.
211. Zhang ZL, Liao YQ, Tang D. Intratumoral microbiota: new frontiers in tumor immunity. *Carcinogenesis* 2022;**43**:719−27.
212. Jiang XT, Xu J, Liu MF, Xing H, Wang ZM, Huang L, et al. Adoptive $CD8^+$ T cell therapy against cancer: challenges and opportunities. *Cancer Lett* 2019;**462**:23−32.
213. Lam KC, Araya RE, Huang A, Chen Q, Modica MD, Rodrigues RR, et al. Microbiota triggers STING-type I IFN-dependent monocyte reprogramming of the tumor microenvironment. *Cell* 2021;**184**:5338−56.
214. 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.
215. Davidsson S, Carlsson J, Greenberg L, Wijkander J, Söderquist B, Erlandsson A. *Cutibacterium acnes* induces the expression of immunosuppressive genes in macrophages and is associated with an increase of regulatory T-Cells in prostate cancer. *Microbiol Spectr* 2021;**9**:e01497-21.
216. Weber R, Groth C, Lasser S, Arkhypov I, Petrova V, Altevogt P, et al. IL-6 as a major regulator of MDSC activity and possible target for cancer immunotherapy. *Cell Immunol* 2021;**359**:104254.
217. Long DL, Liu M, Li HY, Song JH, Jiang XH, Wang G, et al. Dysbacteriosis induces abnormal neurogenesis *via* LPS in a pathway requiring NF-κB/IL-6. *Pharmacol Res* 2021;**167**:105543.
218. 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.
219. Alexander JL, Kohoutova D, Powell N. Science in focus: the microbiome and cancer therapy. *Clin Oncol* 2019;**31**:1−4.
220. Fu YJ, Liu SS, Zeng S, Shen H. From bench to bed: the tumor immune microenvironment and current immunotherapeutic strategies for hepatocellular carcinoma. *J Exp Clin Canc Res* 2019;**38**:396.
221. Wagner J, Rapsomaniki MA, Chevrier S, Anzeneder T, Langwieder C, Dykgers A, et al. A single-cell atlas of the tumor and immune ecosystem of human breast cancer. *Cell* 2019;**177**:1330−45.
222. Alexander JL, Wilson ID, Teare J, Marchesi JR, Nicholson JK, Kinross JM. Gut microbiota modulation of chemotherapy efficacy and toxicity. *Nat Rev Gastro Hepat* 2017;**14**:356−65.
223. Yu TC, Guo FF, Yu YN, Sun TT, Ma D, Han JX, et al. *Fusobacterium nucleatum* promotes chemoresistance to colorectal cancer by modulating autophagy. *Cell* 2017;**170**:548−63.

224. Lehouritis P, Cummins J, Stanton M, Murphy CT, McCarthy FO, Reid G, et al. Local bacteria affect the efficacy of chemotherapeutic drugs. *Sci Rep* 2015;**5**:14554.
225. Panebianco C, Adamberg K, Jaagura M, Copetti M, Fontana A, Adamberg S, et al. Influence of gemcitabine chemotherapy on the microbiota of pancreatic cancer xenografted mice. *Cancer Chemoth Pharm* 2018;**81**:773−82.
226. LaCourse KD, Zepeda-Rivera M, Kempchinsky AG, Baryiames A, Minot SS, Johnston CD, et al. The cancer chemotherapeutic 5-fluorouracil is a potent *Fusobacterium nucleatum* inhibitor and its activity is modified by intratumoral microbiota. *Cell Rep* 2022;**41**:111625.
227. Song WT, Anselmo AC, Huang L. Nanotechnology intervention of the microbiome for cancer therapy. *Nat Nanotechnol* 2019;**14**:1093−103.
228. Sorbara MT, Pamer EG. Microbiome-based therapeutics. *Nat Rev Microbiol* 2022;**20**:365−80.
229. Vargason AM, Anselmo AC. Clinical translation of microbe-based therapies: current clinical landscape and preclinical outlook. *Bioeng Transl Med* 2018;**3**:124−37.
230. Wu F, Liu JY. Decorated bacteria and the application in drug delivery. *Adv Drug Deliv Rev* 2022;**188**:114443.
231. Gao CX, Wang XJ, Yang B, Yuan W, Huang W, Wu GJ, et al. Synergistic target of intratumoral microbiome and tumor by metronidazole-fluorouridine nanoparticles. *ACS Nano* 2023;**17**:7335−51.
232. Trivedi R, Upadhyay TK, Kausar MA, Saeed A, Sharangi AB, Almatroudi A, et al. Nanotechnological interventions of the microbiome as a next-generation antimicrobial therapy. *Sci Total Environ* 2022;**833**:155085.
233. Hussain S, Joo JY, Kang JY, Kim B, Braun GB, She ZG, et al. Antibiotic-loaded nanoparticles targeted to the site of infection enhance antibacterial efficacy. *Nat Biomed Eng* 2018;**2**:95−103.
234. Salama NR, Hartung ML, Müller A. Life in the human stomach: persistence strategies of the bacterial pathogen *Helicobacter pylori*. *Nat Rev Microbiol* 2013;**11**:385−99.
235. Angsantikul P, Thamphiwatana S, Zhang QZ, Spiekermann K, Zhuang J, Fang RH, et al. Coating nanoparticles with gastric epithelial cell membrane for targeted antibiotic delivery against *Helicobacter pylori* infection. *Adv therapeutics* 2018;**1**:1800016.
236. Luo M, Jia YY, Jing ZW, Li C, Zhou SY, Mei QB, et al. Construction and optimization of pH-sensitive nanoparticle delivery system containing PLGA and UCCs-2 for targeted treatment of *Helicobacter pylori*. *Colloid Surfaces B* 2018;**164**:11−9.
237. Hu CMJ, Fang RH, Wang KC, Luk BT, Thamphiwatana S, Dehaini D, et al. Nanoparticle biointerfacing by platelet membrane cloaking. *Nature* 2015;**526**:118−21.
238. Richter AP, Brown JS, Bharti B, Wang A, Gangwal S, Houck K, et al. An environmentally benign antimicrobial nanoparticle based on a silver-infused lignin core. *Nat Nanotechnol* 2015;**10**:817−23.
239. Ling H, Lou XY, Luo QH, He ZG, Sun MC, Sun J. Recent advances in bacteriophage-based therapeutics: insight into the post-antibiotic era. *Acta Pharm Sin B* 2022;**12**:4348−64.
240. Zhang Y, Li CX, Zhang XZ. Bacteriophage-mediated modulation of microbiota for diseases treatment. *Adv Drug Deliv Rev* 2021;**176**:113856.
241. Sheridan C. Genetic medicines aim straight for the heart. *Nat Biotechnol* 2023;**41**:435−7.
242. Dedrick RM, Guerrero-Bustamante CA, Garlena RA, Russell DA, Ford K, Harris K, et al. Engineered *Bacteriophages* for treatment of a patient with a disseminated drug-resistant *Mycobacterium abscessus*. *Nat Med* 2019;**25**:730−3.
243. Duan Y, Llorente C, Lang S, Brandl K, Chu HK, Jiang L, et al. Bacteriophage targeting of gut bacterium attenuates alcoholic liver disease. *Nature* 2019;**575**:505−11.
244. Agarwal R, Johnson CT, Imhoff BR, Donlan RM, McCarty NA, Garcia AJ. Inhaled bacteriophage-loaded polymeric microparticles ameliorate acute lung infections. *Nat Biomed Eng* 2018;**2**:841−9.
245. 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.
246. Dong X, Pan P, Zheng DW, Bao P, Zeng X, Zhang XZ. Bioinorganic hybrid bacteriophage for modulation of intestinal microbiota to remodel tumor-immune microenvironment against colorectal cancer. *Sci Adv* 2020;**6**:eaba1590.
247. Krom RJ, Bhargava P, Lobritz MA, Collins JJ. Engineered phagemids for nonlytic, targeted antibacterial therapies. *Nano Lett* 2015;**15**:4808−13.
248. Li Y, Qu XW, Cao BR, Yang T, Bao Q, Yue H, et al. Selectively suppressing tumor angiogenesis for targeted breast cancer therapy by genetically engineered phage. *Adv Mater* 2020;**32**:e2001260.
249. Skurnik M, Pajunen M, Kiljunen S. Biotechnological challenges of phage therapy. *Biotechnol Lett* 2007;**29**:995−1003.
250. Ji H, Jiang ZT, Wei C, Ma YC, Zhao JH, Wang F, et al. Intratumoural microbiota: from theory to clinical application. *Cell Commun Signal* 2023;**21**:164.
251. Dalile B, Oudenhove LV, Vervliet B, Verbeke K. The role of short-chain fatty acids in microbiota−gut−brain communication. *Nat Rev Gastro Hepat* 2019;**16**:461−78.
252. Paredes-Sabja D, Shen A, Sorg JA. Clostridium difficile spore biology: sporulation, germination, and spore structural proteins. *Trends Microbiol* 2014;**22**:406−16.
253. 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.
254. Cook MT, Tzortzis G, Charalampopoulos D, Khutoryanskiy VV. Microencapsulation of probiotics for gastrointestinal delivery. *J Control Release* 2012;**162**:56−67.
255. Centurion F, Basit AW, Liu JY, Gaisford S, Rahim MA, Kalantar-Zadeh K. Nanoencapsulation for probiotic delivery. *ACS Nano* 2021;**15**:18653−60.
256. Zheng DW, Deng WW, Song WF, Wu CC, Liu J, Hong S, et al. Biomaterial-mediated modulation of oral microbiota synergizes with PD-1 blockade in mice with oral squamous cell carcinoma. *Nat Biomed Eng* 2022;**6**:32−43.
257. Xie AQ, Ji HH, Liu ZY, Wan YQ, Zhang XC, Xiong HH, et al. Modified prebiotic-based "shield" armed probiotics with enhanced resistance of gastrointestinal stresses and prolonged intestinal retention for synergistic alleviation of colitis. *ACS Nano* 2023;**17**:14775−91.
258. Centurion F, Merhebi S, Baharfar M, Abbasi R, Zhang CC, Mousavi M, et al. Cell-mediated biointerfacial phenolic assembly for probiotic nano encapsulation. *Adv Funct Mater* 2022;**32**:2200775.
259. Vargason AM, Santhosh S, Anselmo AC. Surface modifications for improved delivery and function of therapeutic bacteria. *Small* 2020;**16**:e2001705.
260. Cao FF, Jin LL, Gao Y, Ding Y, Wen HY, Qian ZF, et al. Artificial-enzymes-armed *Bifidobacterium longum* probiotics for alleviating intestinal inflammation and microbiota dysbiosis. *Nat Nanotechnol* 2023;**18**:617−27.
261. Zheng DW, Li RQ, An JX, Xie TQ, Han ZY, Xu R, et al. Prebiotics-encapsulated probiotic spores regulate gut microbiota and suppress colon cancer. *Adv Mater* 2020;**32**:e2004529.
262. Lee Y, Sugihara K, Gillilland MG, Jon SY, Kamada N, Moon JJ. Hyaluronic acid-bilirubin nanomedicine for targeted modulation of dysregulated intestinal barrier, microbiome and immune responses in colitis. *Nat Mater* 2020;**19**:118−26.
263. Ouyang J, Deng B, Zou BH, Li YJ, Bu QY, Tian Y, et al. Oral hydrogel microbeads-mediated *in situ* synthesis of selenoproteins for regulating intestinal immunity and microbiota. *J Am Chem Soc* 2023;**145**:12193−205.
264. Chen QB, Li Q, Liang YQ, Zu MH, Chen NX, Canup BSB, et al. Natural exosome-like nanovesicles from edible tea flowers suppress metastatic breast cancer *via* ROS generation and microbiota modulation. *Acta Pharm Sin B* 2022;**12**:907−23.

265. Wang G, Yu Y, Wang YZ, Wang JJ, Guan R, Sun Y, et al. Role of SCFAs in gut microbiome and glycolysis for colorectal cancer therapy. *J Cell Physiol* 2019;**234**:17023−49.
266. Shashni B, Nagasaki Y. Short-chain fatty acid-releasing nano-prodrugs for attenuating growth and metastasis of melanoma. *Acta Biomater* 2023;**159**:226−36.
267. Hsu RYC, Chan CHF, Spicer JD, Rousseau MC, Giannias B, Rousseau S, et al. LPS-induced TLR4 signaling in human colorectal cancer cells increases β1 integrin-mediated cell adhesion and liver metastasis. *Cancer Res* 2011;**71**:1989−98.
268. Song WT, Tiruthani K, Wang Y, Shen LM, Hu MY, Dorosheva O, et al. Trapping of lipopolysaccharide to promote immunotherapy against colorectal cancer and attenuate liver metastasis. *Adv Mater* 2018;**30**:e1805007.
269. Ji GF, Si XH, Dong S, Xu YJ, Li MQ, Yang B, et al. Manipulating liver bile acid signaling by nanodelivery of bile acid receptor modulators for liver cancer immunotherapy. *Nano Lett* 2021;**21**:6781−91.
270. McDonald B, Zucoloto AZ, Yu IL, Burkhard R, Brown K, Geuking MB, et al. Programing of an intravascular immune firewall by the gut microbiota protects against pathogen dissemination during Infection. *Cell Host Microbe* 2020;**28**:660−8.
271. Han SL, Bao XY, Zou YF, Wang LZ, Li YT, Yang LL, et al. D-lactate modulates M2 tumor-associated macrophages and remodels immunosuppressive tumor microenvironment for hepatocellular carcinoma. *Sci Adv* 2023;**9**:eadg2697.
272. Mager LF, Burkhard R, Pett N, Cooke NCA, Brown K, Ramay H, et al. Microbiome-derived inosine modulates response to checkpoint inhibitor immunotherapy. *Science* 2020;**369**:1481−9.
273. Lee ES, Kim SY, Jeong BC, Kim YR, Bae SJ, Ahn OS, et al. A bacterial flagellin, vibrio vulnificus FlaB, has a strong mucosal adjuvant activity to induce protective immunity. *Infect Immun* 2006;**74**:694−702.
274. Zheng JH, Nguyen VH, Jiang SN, Park SH, Tan WZ, Hong SH, et al. Two-step enhanced cancer immunotherapy with engineered *Salmonella typhimurium* secreting heterologous flagellin. *Sci Transl Med* 2017;**9**:eaak9537.
275. Griffin ME, Espinosa J, Becker JL, Luo JD, Carroll TS, Jha JK, et al. Enterococcus peptidoglycan remodeling promotes checkpoint inhibitor cancer immunotherapy. *Science* 2021;**373**:1040−6.
276. Geller LT, Straussman R. Intratumoral bacteria may elicit chemoresistance by metabolizing anticancer agents. *Mol Cell Oncol* 2018;**5**:e1405139.
277. Qiu Q, Lu D, Liu GQ, Yang XY, Li JX, Ren H, et al. Colistin crosslinked gemcitabine micelles to eliminate tumor drug resistance caused by intratumoral microorganisms. *Bioconjug Chem* 2022;**33**:1944−52.
278. Xi JQ, Wang YQ, Gao XJ, Huang YL, Chen J, Chen Y, et al. Reverse intratumor bacteria-induced gemcitabine resistance with carbon nanozymes for enhanced tumor catalytic-chemo therapy. *Nano Today* 2022;**43**:101395.
279. Brennan CA, Garrett WS. *Fusobacterium nucleatum*-symbiont, opportunist and oncobacterium. *Nat Rev Microbiol* 2019;**17**:156−66.
280. Ramos A, Hemann MT. Drugs, bugs, and cancer: *Fusobacterium nucleatum* promotes chemoresistance in colorectal cancer. *Cell* 2017;**170**:411−3.
281. Chen ZX, Li JL, Pan P, Bao P, Zeng X, Zhang XZ. Combination gut microbiota modulation and chemotherapy for orthotopic colorectal cancer therapy. *Nano Today* 2021;**41**:101329.
282. Yan XJ, Ma FH, Chen QX, Gou XB, Li XH, Zhang LW, et al. Construction of size-transformable supramolecular nano-platform against drug-resistant colorectal cancer caused by *Fusobacterium nucleatum*. *Chem Eng J* 2022;**450**:137605.
283. Li XH, Ma YM, Xin YT, Ma FH, Gao H. Tumor-targeting nanoassembly for enhanced colorectal cancer therapy by eliminating intratumoral. *ACS Appl Mater Interfaces* 2023;**15**:14164−72.
284. Chandrangsu P, Rensing C, Helmann JD. Metal homeostasis and resistance in bacteria. *Nat Rev Microbiol* 2017;**15**:338−50.
285. Goss CH, Kaneko Y, Khuu L, Anderson GD, Ravishankar S, Aitken ML, et al. Gallium disrupts bacterial iron metabolism and has therapeutic effects in mice and humans with lung infections. *Sci Transl Med* 2018;**10**:eaat7520.
286. Chitambar CR. The therapeutic potential of iron-targeting gallium compounds in human disease: from basic research to clinical application. *Pharmacol Res* 2017;**115**:56−64.
287. Han ZY, Chen QW, Zheng DW, Chen KW, Huang QX, Zhuang ZN, et al. Inhalable capsular polysaccharide-camouflaged gallium-polyphenol nanoparticles enhance lung cancer chemotherapy by depleting local lung microbiota. *Adv Mater* 2023;**35**:2302551.
288. Zhou SB, Gravekamp C, Bermudes D, Liu K. Tumour-targeting bacteria engineered to fight cancer. *Nat Rev Cancer* 2018;**18**:727−43.
289. Chowdhury S, Castro S, Coker C, Hinchliffe TE, Arpaia N, Danino T. Programmable bacteria induce durable tumor regression and systemic antitumor immunity. *Nat Med* 2019;**25**:1057−63.
290. 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.
291. Wang L, Cao ZP, Zhang MM, Lin SS, Liu JY. Spatiotemporally controllable distribution of combination therapeutics in solid tumors by dually modified bacteria. *Adv Mater* 2022;**34**:e2106669.
292. Canale FP, Basso C, Antonini G, Perotti M, Li N, Sokolovska A, et al. Metabolic modulation of tumours with engineered bacteria for immunotherapy. *Nature* 2021;**598**:662−6.
293. Fan JX, Peng MY, Wang H, Zheng HR, Liu ZL, Li CX, et al. Engineered bacterial bioreactor for tumor therapy *via* fenton-like reaction with localized H_2O_2 generation. *Adv Mater* 2019;**31**:e1808278.
294. Fan JX, Li ZH, Liu XH, Zheng DW, Chen Y, Zhang XZ. Bacteria-mediated tumor therapy utilizing photothermally-controlled TNF-α expression *via* oral administration. *Nano Lett* 2018;**18**:2373−80.
295. Wang G, Kang X, Chen KS, Jehng T, Jones L, Chen J, et al. An engineered oncolytic virus expressing PD-L1 inhibitors activates tumor neoantigen-specific T cell responses. *Nat Commun* 2020;**11**:1395.
296. Suh SB, Jo A, Traore MA, Zhan Y, Coutermarsh-Ott SL, Ringel-Scaia VM, et al. Nanoscale bacteria-enabled autonomous drug delivery system (NanoBEADS) enhances intratumoral transport of nanomedicine. *Adv Sci* 2019;**6**:1801309.
297. Song QL, Zheng CX, Jia JJ, Zhao HJ, Feng QH, Zhang H, et al. A probiotic spore-based oral autonomous nanoparticles generator for cancer therapy. *Adv Mater* 2019;**31**:e1903793.
298. Liang JL, Niu MT, Luo GF, Zhang SM, Huang QX, Jin XK, et al. Tailor-made biotuner against colorectal tumor microenvironment to transfer harms into treasures for synergistic oncotherapy. *Nano Today* 2022;**47**:101662.
299. Chen WF, Wang Y, Qin M, Zhang XD, Zhang ZZ, Sun X, et al. Bacteria-driven hypoxia targeting for combined biotherapy and photothermal therapy. *ACS Nano* 2018;**12**:5995−6005.
300. Zheng PL, Fan M, Liu HF, Zhang YH, Dai XY, Li H, et al. Self-propelled and near-infrared-phototaxic photosynthetic bacteria as photothermal agents for hypoxia-targeted cancer therapy. *ACS Nano* 2021;**15**:1100−10.
301. Wei BC, Pan JM, Yuan RT, Shao BF, Wang Y, Guo X, et al. Polarization of tumor-associated macrophages by nanoparticle-loaded *Escherichia coli* combined with immunogenic cell death for cancer immunotherapy. *Nano Lett* 2021;**21**:4231−40.
302. Geng ZM, Cao ZP, Liu R, Liu K, Liu JY, Tan WH. Aptamer-assisted tumor localization of bacteria for enhanced biotherapy. *Nat Commun* 2021;**12**:6584.
303. Kuerban K, Gao XW, Zhang H, Liu JY, Dong MX, Wu L, et al. Doxorubicin-loaded bacterial outer-membrane vesicles exert enhanced anti-tumor efficacy in non-small-cell lung cancer. *Acta Pharm Sin B* 2020;**10**:1534−48.
304. Cheng KM, Zhao RF, Li Y, Qi YQ, Wang YZ, Zhang YL, et al. Bioengineered bacteria-derived outer membrane vesicles as a versatile antigen display platform for tumor vaccination *via* plug-and-display technology. *Nat Commun* 2021;**12**:2041.

305. Huang WW, Shu CY, Hua LQ, Zhao YL, Xie HH, Qi JL, et al. Modified bacterial outer membrane vesicles induce autoantibodies for tumor therapy. *Acta Biomater* 2020;**108**:300−12.
306. Irene C, Fantappie L, Caproni E, Zerbini F, Anesi A, Tomasi M, et al. Bacterial outer membrane vesicles engineered with lipidated antigens as a platform for *Staphylococcus aureus* vaccine. *Proc Natl Acad Sci U S A* 2019;**116**:21780−8.
307. Guo Q, Li XW, Zhou WX, Chu YC, Chen QJ, Zhang YW, et al. Sequentially triggered bacterial outer membrane vesicles for macrophage metabolism modulation and tumor metastasis suppression. *ACS Nano* 2021;**15**:13826−38.
308. Zhuang WR, Wang YF, Nie WD, Lei Y, Liang C, He JQ, et al. Bacterial outer membrane vesicle based versatile nanosystem boosts the efferocytosis blockade triggered tumor-specific immunity. *Nat Commun* 2023;**14**:1675.
309. Kim OY, Park HT, Dinh NTH, Choi SJ, Lee J, Kim JH, et al. Bacterial outer membrane vesicles suppress tumor by interferon- mediated antitumor response. *Nat Commun* 2017;**8**:626.
310. Chen Y, Liu BY, Wei Y, Kuang DM. Influence of gut and intratumoral microbiota on the immune microenvironment and anticancer therapy. *Pharmacol Res* 2021;**174**:105966.
311. Zheng DW, Chen Y, Li ZH, Xu L, Li CX, Li B, et al. Optically-controlled bacterial metabolite for cancer therapy. *Nat Commun* 2018;**9**:1680.
312. Fukuhara H, Ino Y, Todo T. Oncolytic virus therapy: a new era of cancer treatment at dawn. *Cancer Sci* 2016;**107**:1373−9.