

# Advances in Nanomedicine-Mediated Modulation of the Microbiome for Cancer Therapy

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**Abstract:** The microbiome is closely related to the development of cancer, and it is feasible to modulate the microbiome for cancer therapy. Strategies based on the modulation of the microbiome, such as probiotic therapy and fecal microbiota transplantation (FMT), have achieved certain results in cancer therapy. However, poor targeting and low survival rate of the microbiome limited their further application in cancer therapy. Nanomaterials such as liposomes and micelles are widely used as carriers for drug delivery due to their good biocompatibility and stability. The latest evidence indicates that some nanomedicines can reverse cancer-promoting effects (such as promoting cell proliferation and accelerating tissue inflammation) by eliminating cancer-related microbiota, or increase the proportion of beneficial bacteria, which further enhance the production of beneficial metabolites, facilitate immune cell infiltration, and reshape the tumor microenvironment (TME), thereby inhibit tumor growth. Thus, it is promising to enhance the efficacy of cancer therapy by regulating microbiota through nanomedicines. This review highlights recent advances in the integration of nanomedicine and microbiota modulation for cancer treatment, aiming to provide insights into the design of innovative therapeutic strategies and broaden treatment options for cancer patients.

**Keywords:** nanomedicines, microbiome, digestive cancers, extraintestinal cancers

## Introduction

The global incidence of cancer is on the rise. In 2022, the global cancer landscape was marked by 20 million new cases and 9.7 million deaths. By 2050, the burden is projected to rise by 75% to 35 million cases.<sup>1</sup> Conventional therapy strategies such as surgery, chemotherapy, radiotherapy, and immunotherapy have effectively improved the patient survival rate. However, there remains some limitations including the lack of specificity, the generation of toxic side effects, and drug resistance.<sup>2,3</sup> Tumor epidemiological studies have shown that the microbiome is associated with the incidence of cancer,<sup>4,5</sup> suggesting that the regulation of the microbiome composition is a novel compelling strategy for cancer prevention and therapy.

The microbiome refers to a vast symbiotic microbial ecosystem that inhabit the gastrointestinal tract, mouth cavity, skin, genital tract and other locations,<sup>6,7</sup> containing approximately  $3.8 \times 10^{13}$  microorganisms such as bacteria, fungi, viruses and archaea.<sup>7,8</sup> The maintenance of human health relies on these microorganisms participate in the nutrient absorption of host, immune defense and neuroendocrine regulation through metabolizing dietary fiber to produce short-chain fatty acids,<sup>9</sup> synthesize vitamins,<sup>10</sup> train the immune system,<sup>11</sup> strengthen the mucosal barrier,<sup>12</sup> and regulate the "gut-brain axis".<sup>13</sup> Diversity within microbiome is a core indicator of ecological stability. Dysbiosis caused by microbial composition imbalance is closely related to obesity, metabolic disease, cancer, and mental illness.<sup>14,15</sup> The main way in which the microbiome influences cancer therapy is by reshaping the tumor microenvironment (TME) and regulating immune responses. It is reported that *Fusobacterium nucleatum* enhances the expression of oncogenic genes by activating Toll-like receptor 4 (TLR4) and



triggering nuclear translocation of the nuclear factor- $\kappa$ B (NF- $\kappa$ B), thereby promoting tumor proliferation.<sup>16</sup> *Bifidobacterium* and *Akkermansia muciniphila* have been found to increase the cytotoxic function of T cells by activating CD8<sup>+</sup> T cells and facilitating their infiltration into tumors.<sup>17,18</sup> These studies indicate that the microbiome holds significant value as a therapeutic target for cancer therapy.

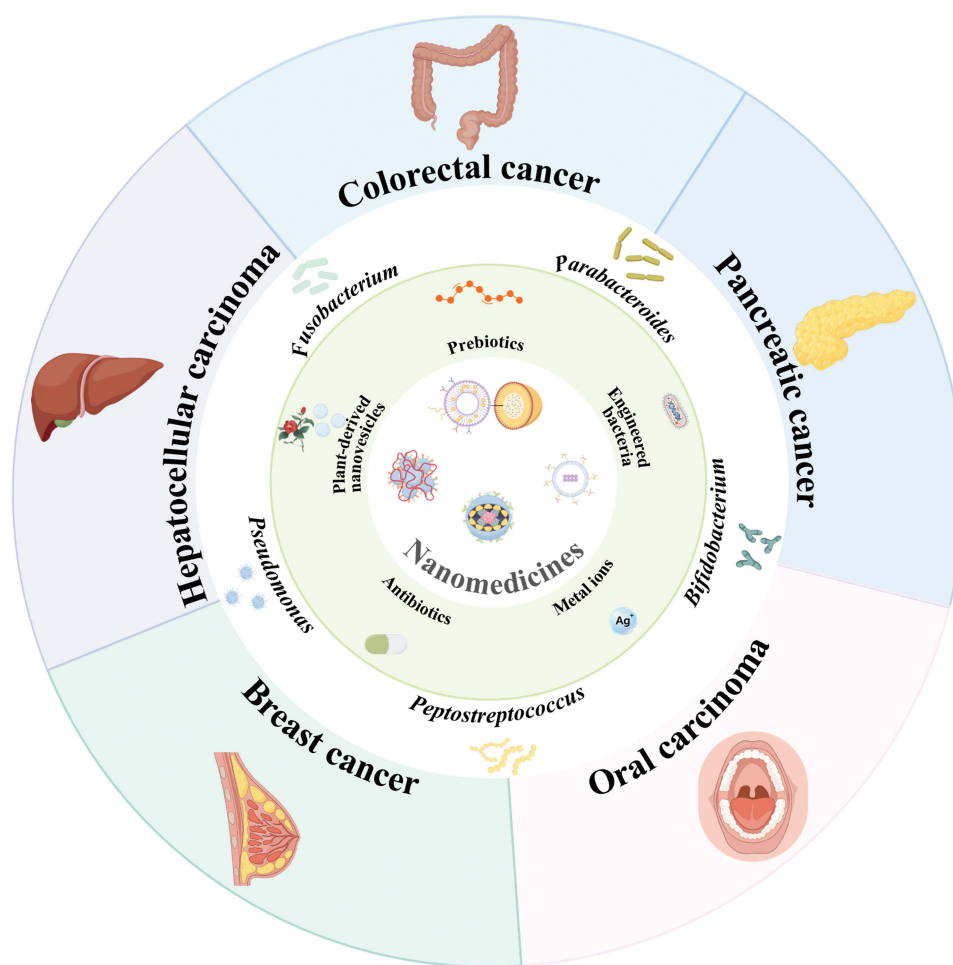
Human commensal microbiota plays a crucial role in tumor immunity, metabolism and treatment response. In recent years, traditional microbial intervention treatments, such as probiotic therapy, antibiotic therapy and fecal microbiota transplantation (FMT), have been widely used in cancer therapy via re-establishing the balance of microbiota. Probiotics, as a type of live and non-pathogenic microorganisms, have shown positive effects in cancer therapy. Clinical evidence demonstrated that *Lactobacillus kefir* LKF01 effectively prevents severe diarrhea symptoms in cancer patients treated with 5-fluorouracil or capecitabine.<sup>19</sup> Ebrahimi et al found that supplementation of bifidogenic live bacterial product CBM588 increased the objective response rate (ORR) of patients with renal cancer by 54% compared with those treated with cabozantinib and nivolumab alone.<sup>20</sup> Similarly, antibiotic metronidazole has also been confirmed to reduce the abundance of *F. nucleatum* in patients with colorectal cancer (CRC), thereby re-sensitizing tumors to immunotherapy.<sup>21</sup> FMT, which transfers the gut microbiota from the healthy individuals to patients, has been demonstrated to be an effective therapy for the treatment of recurrent *Clostridium difficile* infections.<sup>22</sup> Furthermore, an early clinical trial has revealed that FMT from donors who respond to immune checkpoint inhibitors is associated with improved patient outcomes.<sup>23</sup> Although traditional microbial intervention treatments have demonstrated promising efficacy in cancer immunotherapy, several limitations remain, including inadequate targeting specificity, low microbiota survival rate and inconsistent therapeutic outcomes,<sup>23–25</sup> which limit the further application in cancer immunotherapy. Therefore, developing novel strategies to overcome these limitations is imperative.

Nanomaterials, defined as particles with diameters between 1 and 100 nm, can be functionally modified to acquire targeting capabilities and have demonstrated successful applications in targeted cancer therapy.<sup>26</sup> In the last few decades, nanomedicines with microbiota modulating ability have been designed for cancer therapy.<sup>27</sup> This strategy (Figure 1) is able to trigger downstream immune response and inhibit tumor growth by directly eliminating cancer-related microbes or increasing the proportion of beneficial bacteria.<sup>28,29</sup> The reported nanomedicines mainly modulate microbiota through drug-delivery or non-drug delivery strategies. In the regard of drug delivery strategy, Cheng et al reported a bio-responsive micro-nano system based on bovine serum albumin (BSA), which can target lung tissue, brain and infected macrophages, significantly increase the accumulation of drugs in lesions, and effectively eliminate *Cryptococcus neoformans* in the body. Meanwhile, reduce the exposure to normal tissues and symbiotic flora throughout the body, thereby effectively alleviating systemic toxicity.<sup>30</sup> However, there exert a risk of disrupting the balance of the microbiota and inducing drug resistance.<sup>31</sup> In contrast, non-drug delivery strategy that modulate microbiota through physical catalysis or immune regulation is more conducive to maintaining microecological stability.<sup>32</sup> Liu et al developed a nanoparticle-based sonodynamic therapy, effectively generating reactive oxygen species (ROS) to reduce *H. pylori* infection without causing an imbalance in the intestinal microbiota and neutralizing vacuolar cytotoxin A.<sup>33</sup> These studies suggest that the combined therapy of microbiota modulation and nanomaterials is a promising alternative in cancer therapy.

In this review, we systematically explore recent advances in microbiome-modulated nanomedicine for cancer therapeutics, with particular emphasis on: (1) tumor-promoting mechanisms of core microbiota across various cancer types; (2) cutting-edge developments in nanotechnology-based approaches; and (3) their corresponding anticancer mechanisms of action and therapeutic outcomes.

## Microbiome-Modulated Nanomedicines for Digestive Cancer Therapy

Digestive cancers including CRC, hepatocellular carcinoma (HCC), pancreatic cancer (PC), esophageal cancer (EC), and gastric cancer (GC) collectively account for a quarter of global cancer cases and are proved to be the result of the combined effect of genetic and environmental factors. For instance, smoking, high-fat diet, and alcohol consumption are all risk factors for digestive cancers.<sup>34,35</sup> Several microbes, such as *Fusobacterium* species and *Helicobacter pylori*, have been recognized to be associated with the development of digestive cancers.<sup>36,37</sup>



**Figure 1** Schematic diagram of strategies for modulating the microbiome mediated by nanoparticles for tumor treatment.

## CRC

CRC is a major health issue in the human digestive system, accounting for approximately 10% of all cancer cases and is the third most prevalent cancer worldwide.<sup>38</sup> Surgery, chemotherapy, and radiotherapy are the conventional therapeutic modalities for CRC. In the past decade, immunotherapy has attracted great attention as it can fully activate the patients' autoimmune systems to resist cancer, which make up for the low efficiency and poor efficacy of the conventional therapeutic modalities.<sup>39</sup> However, its efficacy is greatly undermined by the immunosuppressive TME and the imbalanced gut microbiota.<sup>40</sup> The latest research reveals that the gut microbiota and its metabolites are involved in the initiation, progression, and therapeutic resistance of CRC.<sup>41</sup> An early metagenomic sequencing study indicated that the diversity of the microbiota in patients with CRC decreased, and the microbiota was imbalanced.<sup>42</sup> It is worth noting that the abundance of some cancer-promoting microbiota in patients with CRC increased significantly.<sup>43</sup>

## Role of the Microbiota in CRC Development

Several species of microbes have been reported to be related to the occurrence of CRC, such as Enterotoxigenic *Bacteroides fragilis* (ETBF), *F. nucleatum*, and *pks+* *Escherichia coli*. ETBF produces the *B. fragilis* toxin, which cleaves E-cadherin and further releases  $\beta$ -catenin to drive c-Myc expression, promoting the proliferation of CRC.<sup>44</sup> *F. nucleatum* is a type of oral anaerobic bacteria that is frequently detected in CRC, which promotes the progression of CRC via mechanisms such as tumor growth, metastasis, immune evasion, metabolic reprogramming and therapeutic resistance.<sup>45</sup> For instance, *F. nucleatum* binds CRC cells and colonizes in tumors by means of the adhesin RadD. RadD further interacts with the CD147 receptor, activating the PI3K-AKT-NF- $\kappa$ B pathway to support tumor growth.<sup>46</sup>

Moreover, research by Nougayrède et al found that colibactin secreted by *pks+* *E. coli* induces DNA double-strand breaks (DSBs) and chromosomal instability, activates the Wnt/ $\beta$ -catenin pathway, which contribute to the development of CRC.<sup>47</sup> Suggesting that the regulation of the microbiome plays a key role in the CRC therapy.

## Microbiome-Modulated Nanomedicines for CRC Therapy

Given the critical involvement of gut microbes in CRC pathophysiology, microbiome-targeted nanomedicines have gained prominence. These nanotherapeutics enhance drug accumulation at tumor sites, modulate local microbiota, and improve antitumor immunity. Strategies are broadly categorized based on nanomaterial composition:

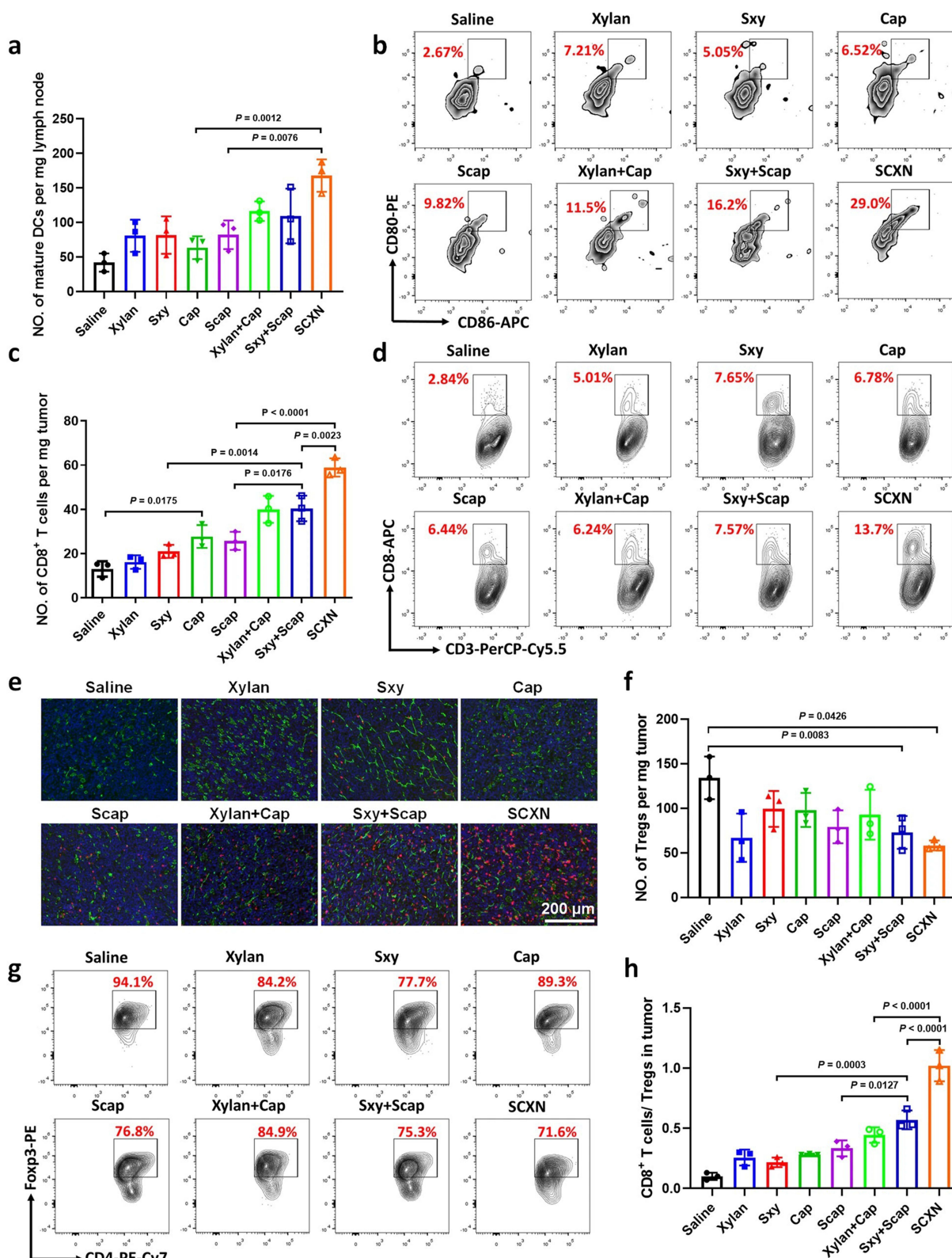
### Liposomes and Protein-Based Nanomedicines

Considering the targeting property of nanomaterials in cancer therapy, and their excellent biocompatibility, nanomaterials are gradually being used for targeted drug delivery. Among these, liposomes and proteins demonstrate superior biocompatibility as naturally occurring components, exhibiting efficient cellular uptake while generating non-toxic metabolic byproducts devoid of adverse effects.<sup>48,49</sup> For instance, a PEGylated liposome was developed for the co-delivery of irinotecan hydrochloride (CPT-11) and Thalidomide (THA), regulating inflammatory cytokines and gut microbiota, and significantly inhibit tumor growth in CRC-bearing mice.<sup>50</sup> Xu et al conjugated *Limosilactobacillus reuteri* (LR) with immunoadjuvant and carbon dot co-loaded plant lipid nanoparticles, which enable precise release of gut residual drugs in tumor areas. And LR metabolizes tryptophan to generate indole-3-aldehyde, which further enhances the anti-tumor immune response and regulates the gut microbiota, increasing the abundance of beneficial microbes.<sup>29</sup> However, the in vivo colonization, proliferation, and genetic stability of engineered bacterium are uncontrollable, the biological safety deserves in-depth exploration. Au@BSA-CuPpIX, an ultrasonic stimulus-responsive albumin nanoplatform with antibacterial function synthesized using BSA as carrier and stabilizer. This nanoplatform can effectively eliminate intratumoral *F. nucleatum*, reduce the level of apoptotic inhibitory proteins, and achieve effective tumor treatment as well as avoid severe inflammation reactions. In vivo mouse experiments further demonstrated that Au@BSA-CuPpIX showed better therapeutic effects on transplanted CRC by eliminating *F. nucleatum* combination with SDT.<sup>51</sup> Zu et al constructed a nanomedicine (Ce6/R837@LP<sub>127</sub>NPs) based on silk protein loaded with chlorin e6 and imiquimod, R837, is coated with a hybrid film composed of plant-extracted lipids and Pluronic F127 on its surface. Which has been demonstrated to stably pass through the gastrointestinal tract, significantly increased the relative abundance of *Parabacteroides* and *Lactobacillus*, further enhance T cell responses and the therapy efficacy of  $\alpha$ PD-L1 against tumors.<sup>52</sup>

### Polymers-Based Nanomedicines

Coincidentally, polymers also widely used as carriers for drug delivery due to their good biocompatibility,<sup>53</sup> which owing higher stability than lipids and proteins.<sup>54,55</sup> Several polysaccharides have been reported for the production of nanomaterials to regulate the microbiome and achieve the CRC therapy. Inulin, a biopolymer approved by the Food and Drug Administration (FDA) for drug delivery, prevents drugs from being affected by the acidic and enzymatic environment in the upper gastrointestinal tract, achieving colon-specific drug release.<sup>56</sup> Nanoparticle (UIRN) prepared by coating regorafenib (REG) with inulin increased the concentration and accumulation time of REG in tumors. After UIRN treatment, the relative abundance of probiotics in the colon increased, accompanied by a decrease in the proportion of tumor-promoting flora.<sup>57</sup> Inulin promotes the accumulation of drugs at the lesion site by strengthening the adhesion of organisms and prolonging their retention time in the colon. Leading to the secretion of inulin enzymes and specifically degrade inulin, thereby generating short-chain fatty acids (SCFAs) and further reshaping the intestinal microenvironment and intratumoral microbiota. Meanwhile, the degradation of inulin promotes the targeted exposure of nanomedicines at CRC sites, effectively inhibiting tumor growth.<sup>32</sup> This is a novel strategy that utilizes in situ microbiota to activate antigen-presenting function, but it is necessary to consider how to precisely utilize intratumoral bacterial antigens without causing harmful inflammation.

Besides inulin, Lang et al constructed a capecitabine (Cap)-loaded nanoparticle composed of prebiotic xylan-stearic acid conjugate (SCXN). Compared with free Cap, SCXN promoted anti-tumor immune responses through the modulation of gut microbiota. Specifically, SCXN enhanced the number of the matured dendritic cells (Figure 2A and B), further strengthen the ability to recognize tumors. Subsequently, SCXN recruited more CD8<sup>+</sup> T cells into the interior of tumors



**Figure 2** SCXN promotes the anti-tumor immune responses. Analysis of the numbers of immune cells in CT-26 tumor-bearing mice treated with multi-doses of different formulations via flow cytometry or immunofluorescence assay. Numbers (A) and percentages (B) of mature dendritic cells (DCs; CD80<sup>+</sup>CD86<sup>+</sup> cells gated on CD11c<sup>+</sup> cells) in draining lymph nodes. (C) Numbers of the CD8<sup>+</sup> T cells per mg of tumor. (D) Percentage of CD8<sup>+</sup> T cells in the total CD3<sup>+</sup> cell population in tumors. (E) Immunofluorescence images of tumor sections to examine the CD8<sup>+</sup> T cells (red fluorescence) infiltration. Green fluorescence: CD31. Scale bar: 200 μm. Numbers (F) and percentage (G) of regulatory T cells (Tregs, CD4<sup>+</sup>Fosp3<sup>+</sup> cells gated on CD3<sup>+</sup>CD4<sup>+</sup> cells) in tumors. (H) Ratio of CD8<sup>+</sup> T cells to Tregs in tumors. Data represent the mean ± SD (n = 3 mice). Statistical significance was calculated using one-way ANOVA with Tukey's multiple comparisons test. Source data are provided as a Source Data file.<sup>56</sup> © 2023. Springer Nature Limited.

and effectively activated anti-tumor response (Figure 2C–E). Meanwhile, relieved immunosuppression by significantly reduced the proportions of regulatory T cells in the tumor tissues (Figure 2F–H). Furthermore, promotes the proliferation of probiotics and the production of SCFAs to facilitate the anti-cancer immune responses. Ultimately, achieved the combined application of chemotherapy and the modulation of gut microbiota in CRC therapy.<sup>58</sup> A recent study revealed that drug conjugated onto dextran for targeted therapy of CRC, not only was the gut microbiota modulated with dextran but also the retention of the drug in CRC tissues was prolonged, the accumulation of salicylic acid (SA) was significantly increased, and severe inflammation was effectively alleviated.<sup>59</sup> Similarly, a nanomedicine composed of tellurium-containing polycarbonate and cisplatin efficiently killed intratumoral *F. nucleatum* via a membrane destruction mechanism and alleviated the proliferation and inflammatory response of cells at the tumor site.<sup>28</sup>

## Inorganic Nanomedicines

Inorganic nanomaterials possess an ultra-high loading capacity of drugs due to their high stability and porous structure.<sup>60</sup> They can be endowed with good biocompatibility or antibacterial capabilities by different surface modification schemes, thereby better involved into the regulation of gut microbiota for CRC therapy.

Mesoporous silica nanoparticles (MSNs) is a type of inorganic nanomaterial with ordered mesoporous structure and high specific surface area. The surface of MSNs can functionally modified through chemical reactions to exhibit stable chemical properties in the physiological environment.<sup>61</sup> For instance, the surface of 6-gingerol-loaded MSNs was functionalized using mulberry leaf-extracted lipids and Pluronic F127. This nanomedicine safely passed to the colorectal lumen, infiltrated the mucus barrier and penetrates into the deep tumor. It further activates anti-tumor immunity and inhibits tumor growth, significantly increases the abundance of beneficial bacteria, and enhances lipid oxidation metabolites.<sup>62</sup> Chen et al reported an anti-CRC gel, briefly, the CRC chemotherapy drugs metronidazole and 5-fluorouracil were individually incorporated into the MSNs coated with metal polyphenol network, and blended with carboxymethyl cellulose. This anti-CRC gel enhances the elimination of CRC-related microbiota *F. nucleatum* via chemotherapy, effectively inhibiting the growth and metastasis of CRC in an orthotopic mouse model.<sup>63</sup> Another study designed a coordination-redox strategy to enable the homogeneous in-situ growth of antibacterial ultrasmall silver nanoparticles into the dendritic MSNs, further strengthen the drug loading and antibacterial capacity. By this strategy, the side effects of the drug on mice were alleviated, and the antibacterial drug regulated autophagy of CRC cells to induce chemoresistance by eliminating intratumoral *F. nucleatum*, further suppressed the growth of CRC tumor, thereby enhancing therapeutic effects.<sup>64</sup> Although the ultrasmall size of silver nanoparticles is conducive to penetrating tumors, it also increases the risk of entering normal cells,<sup>65</sup> which lead to organelle damage and DNA destruction. Thus, it is necessary to explore the minimum effective dose and evaluate its long-term safety.

Several other inorganic nanomaterial drug delivery strategies have also influenced the CRC therapy by regulating the microbiome. Copper oxide coated onto the surface of PEGylated zinc oxide nanoparticles, and PD-L1 antibodies were used in combination for CRC therapy, the proportion of beneficial microbes such as *Bifidobacterium* was increased and the growth of both in situ and distant tumors was inhibited.<sup>66</sup> Luo et al prepared Prussian Blue nanoparticles loaded with cinobufagin, and the surface was further coated with hybrid cell membranes, which endow the nanoparticles with immune escape and tumor homing capacity. In vitro and in vivo experiments demonstrated that the nanoparticles regulated the gut microbiota of CRC tumor-bearing mice to a normal level and inhibited the metastasis of the primary site by down-regulating the expression of Vimentin, matrix metalloproteinase-9 (MMP-9), and hypoxia-inducible factor-1  $\alpha$  (HIF-1 $\alpha$ ).<sup>67</sup>

In brief, the sole drug therapy of CRC mainly faces the challenges of limited drug accumulation in the tumor site and nonspecific toxicity. In contrast, nanomedicines significantly increased drug accumulation as well as regulated the CRC-related microbiota, superior therapeutic effects were obtained.

## HCC and PC

HCC, as the fifth most common cancer worldwide, is projected to become the third leading cause of cancer-related deaths by 2030.<sup>68</sup> Despite advances in therapeutic, the overall 5-year survival rate remains below 20%, which attributed to the failure of the entire cancer treatment continuum.<sup>69,70</sup> Similarly, as a highly lethal malignant tumor, the 5-year overall

survival rate of PC is less than 10% due to the lack of effective therapy strategies.<sup>71</sup> Recent research revealed that the development of both types of cancer may be related to the imbalance of microbiota.

## Role of the Microbiota in HCC and PC Development

The vast majority of HCC occur in patients with liver cirrhosis. The leaky gut and dysbiosis are the prominent characteristics of liver cirrhosis, reflected by increased incidence of gut-derived bacterial infections, which further promote gradual progression of fibrosis, liver cirrhosis and HCC.<sup>72</sup> Early studies have shown an increase in bacterial diversity in HCC patients,<sup>73</sup> and the *genus Turicibacter* was a protective factor for HCC.<sup>74</sup> Recently, Balcik-Ercin et al indicated that the treatment of *Lactococcus* and *Streptococcus* species led to the down-regulation of TWIST1 expression in HCC, which affect the transformation from epithelial cells to mesenchymal cells.<sup>75</sup> Gut microbiota products and their translocations play a key role in the formation of HCC cells proliferation by TLR4 on macrophages through lipopolysaccharides (LPS).<sup>76</sup>

For PC, the key virulence factor of Gram-positive bacteria – lipoteichoic acid (LTA) – triggers the excessive secretion of pro-inflammatory factors by binding to CD14 or Toll-like receptor 2 (TLR2) and may be involved in the progression of PC in mice infected with *Enterococcus faecalis*.<sup>77,78</sup> Deoxycholic acid (DCA), a microbial metabolite produced by 7 $\alpha$ -dehydroxylating bacteria and secondary bile acids, also exhibited an enhanced ability for the induction of PC.<sup>79</sup> These evidences suggest that it is feasible to treat HCC and PC by modulating the gut microbiota.

## Nanomedicines Combined with Microbiota Modulation in HCC and PC

Liver inflammation and immunosuppressive TME are crucial for HCC and metastasis. A latest study designed a dextran-glycyrrhetic acid conjugate to precisely deliver glycyrrhetic acid to tumor sites, which significantly reduced the abundance of lipopolysaccharide-related microbiota, increased natural killer T cells and CD8<sup>+</sup> T cells, and decreased the proportion of M2 macrophages, ultimately led to an increase in tumor suppression rate.<sup>76</sup> However, the therapeutic effect depends on the original microbiota baseline of host, with significant individual differences.

The dense extracellular matrix (ECM) in PC restricts drug penetration, whereas, the adoption of nano-strategies can make up for this deficiency. Recently, Yao et al developed a tumor-targeting probiotic-nanosystem, which inhibited the formation of ECM by silence the active pancreatic stellate cells (PSC), thereby remodeling ECM to facilitate the penetration of drugs and immune cells. Meanwhile, this probiotic-nanosystem selectively regulated the tumor-colonizing microbiota. The tumor infiltration and the tumoricidal immunity remarkably enhanced under this synergistic effect.<sup>80</sup> These findings highlight the potential of microbiome-modulated nanomedicines in remodeling the TME and improving the efficacy of malignancies.

## Microbiome-Modulated Nanomedicines for Extraintestinal Cancers

Gut microbiota not only play a crucial role in digestive cancers but also influence the development of extraintestinal cancers, such as breast cancer (BC) and oral squamous cell carcinoma (OSCC). Initial success has been achieved in reducing the incidence of extraintestinal cancers by interrupting the harmful host-microbe network through the use of antibiotics and targeted molecular therapies.<sup>81</sup> Here, we review the strategies adopted in recent years to regulate the microbiome for the treatment of extraintestinal cancers through nanotherapy.

### BC

BC is the most common malignant tumor in women. Statistically, the number of new cases exceeded 2.05 million in 2018, ranking second among all instances of cancer.<sup>82</sup> Approximately 20% of BC lack expression of human epidermal growth factor receptor 2 (HER2), and estrogen receptor (ER)/progesterone receptor (PR), called triple-negative breast cancer (TNBC). Which develop resistance to chemotherapy due to their high invasiveness.<sup>83</sup> Although traditional surgery, radiotherapy and chemotherapy have significantly improved the survival rate of patients, some patients diagnosed at an early stage still develop metastatic diseases.<sup>84</sup> It is urgent to development more effective strategies for BC therapy.

## Role of the Microbiota in BC Development

The latest research acknowledges the existence of a unique microbiome in breast tissue, including bacteria from the *Proteobacteria*, *Firmicutes* and *Actinobacteria* phyla, which differs in healthy and cancerous breast tissue.<sup>85</sup> A large amount of evidence supports that the dysregulation of the microbiome affects the development of BC through direct or indirect signaling pathways. For instance, the abundance of *Staphylococcus* increased in BC tissues, which is negatively correlated with the expression of the oncogene TRAF4, enhancing the activation of T-cell genes related to microbe. However, the accumulation of some microbe, such as *Propionibacterium acnes*, which conducive to the activation of T cells but expressed at a low level in BC tissues.<sup>86,87</sup> The flagellin of *Salmonella typhimurium* has been found to activate the innate immune response in BC patients and mark Toll-like receptor 5 (TLR5) as a therapeutic target.<sup>88</sup>

## Nanomedicines Combined with Microbiota Modulation in BC

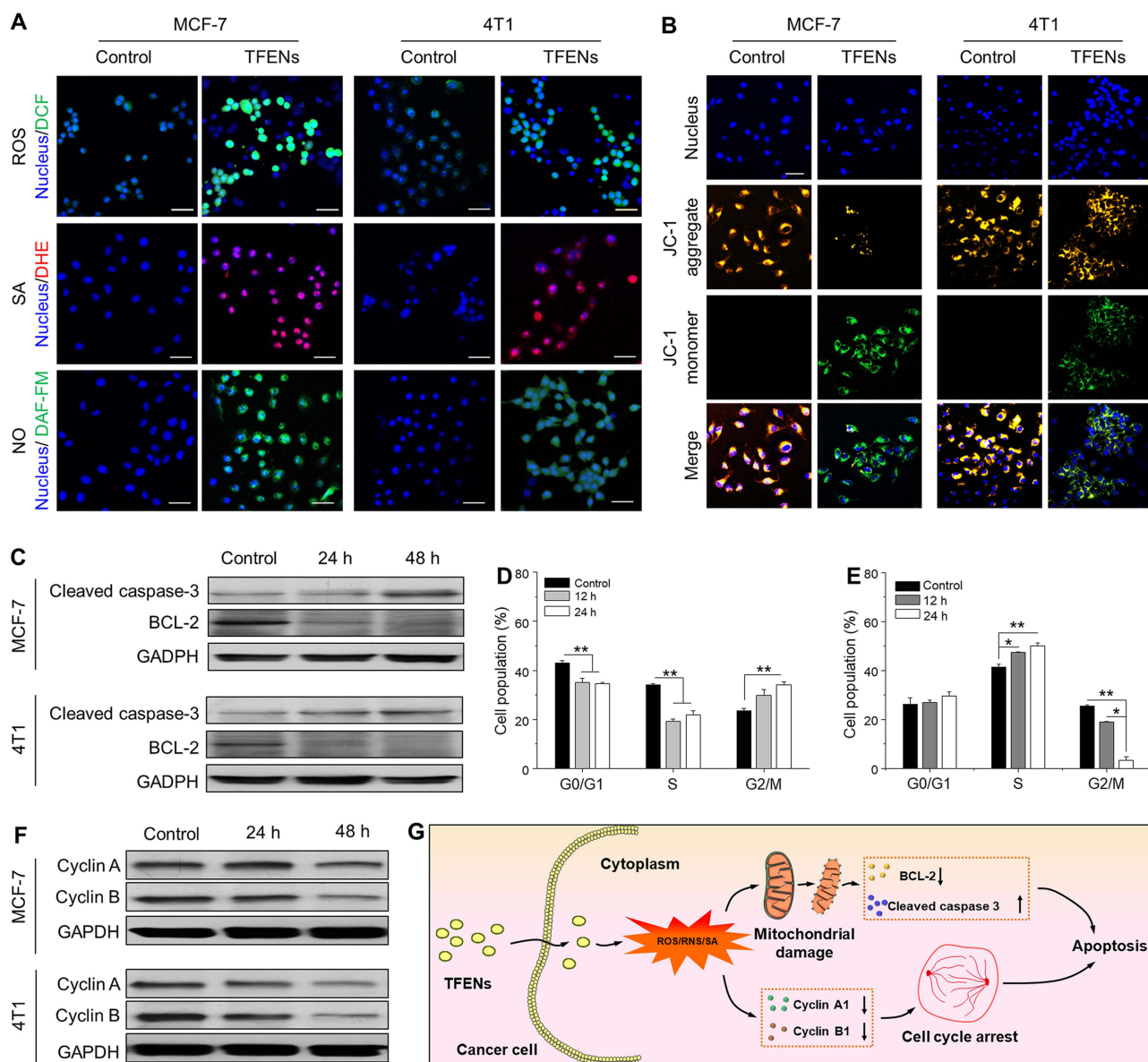
The tumor heterogeneity of BC (including the TME and breast cancer stem cells (BCSC)) is one of the prominent factors leading to chemotherapy failure and drug resistance.<sup>89</sup> Nanomaterials have demonstrated advantages in the BC therapy due to their small size, active and passive targeting, and controlled release properties.<sup>83</sup> In a study on the BC therapy with the combination of antibiotics (ABX) and liposomal doxorubicin (LipoDox), ABX regulated the gut microbiota of mice bearing TNBC cells, further altering the biodistribution curve of nanoparticles and increasing the accumulation of LipoDox in tumors, thereby enhancing the long-term anti-tumor efficacy.<sup>90</sup> Suggesting that the regulation of the gut microbiota combined with the nanomedicine-based therapeutics may improve the therapeutic effect of BC. In recent years, several research have focused on the development of nanomedicines with the potential to regulate microbial ecology and enhance anti-tumor immune responses during the BC therapy. Among them, natural nanomaterials derived from plants are remarkable. Plant-derived exosome-like nanovesicles contain large amounts of polyphenols, flavonoids, functional proteins, and lipids. Chen et al demonstrated that plant-derived exosome-like nanovesicles stimulate the generation of oxidative stress in BC cells. Specifically, plant-derived exosome-like nanovesicles promoted the reaction of highly ROS amplification, increased the level of NO, and triggered mitochondrial damage to release cytochrome C (Figure 3A and B). Further exploration found that TFENs activated the mitochondrial-mediate apoptosis by down-regulate BCL-2 expression and upregulate Cleaved caspase-3 expression (Figure 3C). Moreover, TFENs disturbed cell cycle, which inhibit the mitosis process or block DNA replication (Figure 3D–F). Synergistically resulting in the inhibition of BC growth and metastasis as well as the modulation of the gut microbiota.<sup>91</sup> Plant-derived exosome-like nanovesicles also exhibited excellent stability and tolerance to acidic digestion. Thus, whether administered orally or intravenously, the significant therapeutic effects were exerted by enhancing the systemic anti-tumor immune response and regulating the gut microbiota.<sup>92</sup> Notably, significant hepatorenal toxicity as well as immune activation were observed when administered by intravenous injection.<sup>93</sup> These findings highlight the advantages of plant-derived exosome-like nanovesicles as effective candidates for BC treatment. However, the active ingredients of these nanovesicles are complex and lack a clear dose-effect relationship, which face huge challenges in the clinical transformation.

## OSCC

As the most destructive oral cancer, the overall 5-year survival rate of OSCC still less than 50%.<sup>94</sup> At present, chemotherapy remains a common treatment for OSCC. However, the existence of drug resistance hinders the efficacy of chemotherapy.<sup>95</sup> Thus, new strategies are urgent needed to address this issue for more effective treatment outcomes.

## Role of the Microbiota in OSCC Development

Oral microbiota is closely related to the development of OSCC, which symbiotically modulates the physiology of the host. It is reported that the oral microbiota of OSCC patients is more diverse than that of healthy people. Specifically, the oral microbiota ecology of OSCC patients is imbalanced, and *Porphyromonas* and *F. nucleatum* are significantly increased, which endow resistance to chemotherapy drugs by activating specific signaling pathways such as STAT and NF- $\kappa$ B.<sup>96–99</sup> *Pseudomonas gingivalis* promotes tumor development by inducing a non-ecological inflammatory micro-environment, inhibiting apoptosis, increasing cell proliferation, enhancing angiogenesis, activating epithelial-



**Figure 3** Confocal microscopy images of (A) ROS, SA, NO, and (B) mitochondrial membrane potential changes in MCF-7 cells and 4T1 cells after the treatment of TFENs for 4 h (scale bar: 50 nm). (C) Western blot analysis of cleaved caspase-3 and BCL-2 in MCF-7 cells and 4T1 cells receiving the treatment of TFENs for 24 and 48 h, respectively. Cell population profiles of (D) MCF-7 and (E) 4T1 cells in various cell cycle phases after co-incubation for 12 and 24 h, respectively. Each point represents the mean SEM (n = 3). \*p < 0.05, \*\*p < 0.01. ns, no significance. (F) Western blot analysis of cyclin A and cyclin B in MCF-7 cells and 4T1 cells receiving the treatment of TFENs for 24 and 48 h, respectively. (G) Schematic illustration of the pro-apoptotic mechanism of TFENs against cancer cells.<sup>91</sup> © 2022 Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences. Production and hosting by Elsevier B.V.

mesenchymal transition, and generating carcinogenic metabolites. Additionally, *P. gingivalis* and *F. nucleatum* possess synergistic pathogenicity in oral cancer models in vivo. Whereas, oral streptococcus antagonizes the tumorigenic epithelial cell phenotype induced by *P. gingivalis*.<sup>100</sup> These findings highlight that therapy for regulating these disease-specific microbiota is feasible.

## Nanomedicines Combined with Microbiota Modulation in OSCC

Considering the impact of host-microbiota interaction on the host immune system, the microbiota modulation strategy is effective in OSCC treatment. It has been found that *Peptostreptococcus* could activate the immune system and improve the prognosis of patients. A newly developed adhesive hydrogel containing silver nanoparticles combination with

exogenous bacteria, upregulated the levels of *Peptostreptococcus*, enhanced the anti-tumor immune response, and combated the blockade of immune checkpoints.<sup>101</sup> In another study, the antibacterial properties of nanovesicles extracted from ginger were utilized to specifically target and eliminate *P. gingivalis* enriched in OSCC, down-regulate the IL-6/pSTAT3/P-gp pathway, reduced chemotherapy resistance and enhanced the tumor cell-killing ability of drug.<sup>102</sup>

## The Therapeutic Mechanism of Microbiome-Modulated Nanomedicines

Microbiome-modulated nanomedicines exhibit promising application prospects in tumor therapy, Table 1 summarized the formulations, model systems, target microbes, microbial regulators, and therapeutic mechanism related to microbes of various microbiome-modulated nanomedicines. One of the most direct strategies is to eliminate cancer-related microbes. For instance, *F. nucleatum* is recognized to be closely associated with the progression of CRC,<sup>14</sup> while *P. gingivalis* is the crucial pathogenic bacterium of OSCC.<sup>99</sup> Microbiome-modulated nanomedicines exert the specific function of eliminating cancer-related microbes via targeted delivery of antibiotics, antimicrobials, or by using physical therapies. Further reverse the cancer-promoting effects mediated by these microbes, such as the activation of pro-inflammatory signaling pathways (TLR4/MyD88/NF- $\kappa$ B,<sup>51</sup> IL-6/pSTAT3/P-gp<sup>102</sup>), induction of chemotherapy resistance, inhibition of cell apoptosis, and promotion of cell proliferation. Thereby, effectively restore the sensitivity of cancer to conventional therapy and achieve anti-tumor effects. Moreover, combined anticancer and antibacterial therapeutic effects were further realized by target deliver chemical drugs such as cisplatin<sup>28</sup> and paclitaxel<sup>102</sup> to the tumor site simultaneously.

Depart of directly eliminating cancer-related microbes, more research focused on regulating the structure of microbes, especially enhancing the abundance of beneficial microbes. Among the existing research, the diversity of microbiota was enriched via the self-components of nano-particles (such as plant-derived exosome-like nanovesicle, nanomaterials combined with prebiotic), or deliver immunomodulators utilizing engineered bacterium. Specifically, the proportion of harmful bacteria such as *Bacteroides* and *Alloprevotella* was reduced, while the growth of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* was promoted. Subsequently, increased the levels of beneficial metabolites including SCFAs (produced

**Table 1** Microbiome-Modulated Nanomedicines and Their Cancer Therapeutic Mechanism

Nanomaterial	Formulation	Cancer	Model System	Microbe	Microbial Regulators	Therapeutic Mechanism Related to Microbiota	Reference
<b>Eliminate Cancer-Related Microbiota</b>							
Au@BSA-CuPpIX	Protein	CRC	Mice bearing HCT116 tumor xenografts	<i>F. nucleatum</i>	Antibacterial metalloporphyrin (CuPpIX) sonosensitizer	Prevents the activation of the TLR4/MyD88/NF- $\kappa$ B pathway, reduces the levels of apoptosis-inhibiting proteins, enhances ROS-induced apoptosis.	[51]
PTE@CDDP	Inorganic nanomaterial	CRC	The human CRC cell line-derived mice xenograft model	<i>F. nucleatum</i>	Micromolecular telluride antimicrobials	Reverses <i>F. nucleatum</i> -promoted cell proliferation, reduces the expression of the pro-inflammatory cytokines TNF- $\alpha$ and IL-1 $\beta$ , inhibits tissue inflammation cause by bacteria.	[28]
AB-Gel	Inorganic nanomaterial	CRC	CRC mouse model	<i>F. nucleatum</i>	Antibiotic-metronidazole	Prolongs drug release time and inhibits the progression, metastasis and chemotherapy resistance of CRC by the elimination of <i>F. nucleatum</i> .	[63]
Ag@DMSNs	Inorganic nanomaterial	CRC	Mice	<i>F. nucleatum</i>	Antibacterial ultrasmall silver nanoparticles	Blocks <i>F. nucleatum</i> -induced autophagy activation, relieves the chemotherapy resistance.	[64]
GDNVs	Plant-derived exosome-like nanovesicle	OSCC	Mice	<i>P. gingivalis</i>	The self-components of ginger biologically derived nanovesicles	Attenuates <i>P. gingivalis</i> -mediated drug resistance via down-regulates IL-6/pSTAT3/P-gp signaling axis and augments tumor cell killing.	[102]

(Continued)

Table I (Continued).

Nanomaterial	Formulation	Cancer	Model System	Microbe	Microbial Regulators	Therapeutic Mechanism Related to Microbiota	Reference
<b>Enhance the Abundance of Beneficial Microbiota/Regulate the Structure of Microbiota</b>							
LR-S-CD/ CpG@LNP	Liposome	CRC	Orthotopic CRC mouse model	<i>Lactobacillus</i> , <i>Alistipes</i> , and etc.	Engineered bacterium	Enhances the antitumor immune responses by upregulation the level of indole-3-aldehyde through the tryptophan metabolic pathway.	[29]
UIRN	Polymer	CRC	CT26 tumor mouse model, CRC mouse model	<i>Akkermansia</i> , <i>Parabacteroides</i> , <i>Helicobacter</i> , and etc.	Prebiotic-inulin	Converts inulin into SCFAs under the decomposition and metabolism by gut microbiota, further protects the mucosal barrier and regulates activity of intestinal immune cells.	[57]
SCXN	Polymer	CRC	Colon tumor- bearing mice	<i>Bifidobacterium</i> , <i>Akkermansia</i> , <i>Faecalibaculum</i> , and etc.	Prebiotic-inulin	Promotes the production of SCFAs and built a tumor-suppressing and beneficial microorganism-supporting intestinal microenvironment.	[58]
P3C-Asp	Polymer	CRC	CRC mouse model	<i>Lactobacillus</i> , <i>Akkermansia</i> , <i>Bacteroides</i> , and etc.	Prebiotic-dextran	Generates SCFAs in the intestine and promotes CD8 <sup>+</sup> T cells activation. Alleviates microbial-dependent inflammation and relieves treatment resistance.	[59]
P <sub>127</sub> -MLL@GINS	Inorganic nanomaterial	CRC	CRC mouse model	<i>Bacillus</i> , <i>Bacteroides</i> , <i>Alloprevotella</i> , and etc.	6-gingerol	Promotes the production of linolenic acid metabolites, regulates intestinal homeostasis and facilitates TCA-related apoptosis and ferroptosis-mediated LPO.	[62]
DEX-CBX	Polymer	HCC	Orthotopic HCC- bearing mice	<i>Helicobacter</i> , <i>Akkermansia</i> , and etc.	Prebiotic-dextran	Suppresses LPS-mediated TLR4 activation, alleviates hepatic inflammation caused by LPS, relieves tumor immunosuppressive TME.	[76]
Lipodox	Liposome	BC	Mice	<i>Bacteroidota</i> , <i>Firmicutes</i> , <i>Proteobacteria</i> , and etc.	Antibiotic- doxorubicin	Increases vascular permeability and impairs angiogenesis.	[90]
TFENs	Plant-derived exosome-like nanovesicle	BC	Mouse lung metastasis model of BC	<i>Firmicutes</i> , <i>Bacteroidetes</i> , and etc.	The self- components of tea flowers nanovehicles	Modulates the balance of intestinal microbiota, inhibits the migration of tumor cells into the lymph nodes or circulatory system.	[91]
PGEVs	Plant-derived exosome-like nanovesicle	BC	TNBC tumor- bearing mice model	<i>Bacteroides</i> , <i>Lactobacillus</i> , <i>Firmicutes</i> , and etc.	The self- components of <i>Platycodon</i> <i>grandiflorum</i> - derived extracellular vesicles	Increases the abundance and diversity of the gut microbiota and correct microbiota disorders, further suppresses tumor development.	[92]
TLNTs	Polymer	CRC	BC mouse model	<i>Alistipes</i> , <i>Oscillibacter</i> , <i>Alloprevotella</i> , and etc.	The self- components of tea leaves exosome-like nanotherapeutics	Enriches the diversity of the intestinal microbiota and enhances the anti-tumor immune function.	[93]
AgNP	Polymer	OSCC	C3H-HeN mice	<i>Peptostreptococcus</i> , <i>Streptococcus</i> , <i>Pseudomonas</i> , and etc.	Ag <sup>+</sup>	Regulates the oral microbiota, enhances proliferation of <i>Peptostreptococcus</i> while inhibits the growth of competing bacteria.	[101]

(Continued)

Table I (Continued).

Nanomaterial	Formulation	Cancer	Model System	Microbe	Microbial Regulators	Therapeutic Mechanism Related to Microbiota	Reference
<b>Reshape the Tumor Microenvironment</b>							
Oxa@HMI	Polymer	CRC	CRC tumor-bearing mice	<i>Lactobacillus</i> , <i>Akkermansia</i> , <i>Bacteroidota</i> , and etc.	Prebiotic-inulin	Normalizes microbiota and produces butyric acid to promote the infiltration of CD8 <sup>+</sup> T cells into tumor tissues, ultimately boosts T cell-mediated antitumor immune responses.	[32]
CD@V and CD@G	Liposome	PC	PC tumor-bearing mice	<i>Proteobacteria</i> and <i>Firmicuts</i>	Engineered probiotic	Reduces the contents of tumor-colonizing $\gamma$ -proteobacteria to inhibit the degradation of gemcitabine.	[80]
<b>Synergistic Killing/Induce Immunogenic Death</b>							
CPT-11 and THA Co-Loaded Liposome	Liposome	CRC	CRC tumor-bearing mice	<i>Lachnospiraceae</i> , <i>Colidextribacter</i> , and etc.	-	Improves the gut microbiota imbalance to facilitate the repair of colon damage.	[50]
Ce6/R837@Lp127NPs	Protein	CRC	CRC tumor-bearing mice	<i>Helicobacter</i> , <i>Parabacteroides</i> , <i>Lactobacillus</i> , and etc.	-	Increases the richness of gut microbiota, augments T cell responses, induces Th1-mediated immune reactions, inhibits the growth of orthotopic colon tumors.	[52]
CuxO@ZnO	Inorganic nanomaterial	CRC	Orthotopic CRC-bearing mice	<i>Bifidobacterium</i> , <i>Romboutsia</i> , and etc.	-	Rebalances the intestinal microbiota toward beneficial species.	[66]
PC NPs	Inorganic nanomaterial	CRC	CRC tumor-bearing mice	<i>Bacteroidota</i> , <i>Proteobacteria</i> , <i>Fusobacetriota</i> , and etc.	-	Reverses the decrease of beneficial bacteria and the enrichment of harmful bacteria in the intestine of in tumor-bearing mice was, inhibits CRC growth.	[67]

**Abbreviations:** CRC, colorectal cancer; *F. nucleatum*, *Fusobacterium nucleatum*; OSCC, oral squamous cell carcinoma; *P. gingivalis*, *Pseudomonas gingivalis*; HCC, hepatocellular carcinoma; BC, breast cancer; PC, pancreatic cancer.

through the metabolism by gut microbiota of prebiotic),<sup>103</sup> indole-3-aldehyde (produced through regulate the tryptophan metabolic pathway),<sup>104</sup> or linolenic acid. Further created a tumor-suppressing microenvironment by protecting the mucosal barrier, increasing vascular permeability, or other means, thereby enhancing the anti-tumor response. Similarly, additional drugs like regorafenib, capecitabine, and aspirin were delivered in some strategies, and the intratumoral concentration and accumulation of drugs were increased, which exert synergistic effect of microbiota modulation and chemotherapy. Nanomedicines were also be designed to reshape the TME by regulating the structure of microbes, since the immunosuppression and physical barriers of TME are significant obstacles to cancer therapy.<sup>105,106</sup> For instance, the engineered probiotic system colonized within the tumor expresses matrix-degrading enzymes, reduced collagen density, and promoted the infiltration of immune cells.<sup>80</sup> Hydrogels are used to capture and present microbial antigens within the tumor, thereby stimulating a strong in situ vaccine effect and reversing the immunosuppressive state.<sup>32</sup>

In addition, the core strategy of some nanomedicines is not to directly target microbiota, but to directly kill or induce immunogenic cell death through more effectively delivering chemotherapy drugs, generating ROS, or in combination with physical therapy. It is worth noting that these nanomedicines have also been proven to cause structural changes in the gut microbiota, which combination with the direct killing effect of the delivered drugs and further enhanced the anti-tumor responses. For example, while sonodynamic induction of immunogenic cell death and activation of in situ vaccine effects occur, the accompanying changes in the microbiota may enhance systemic anti-tumor immunity.<sup>52</sup> Photothermal chemotherapy down-regulates metastasis-related proteins such as Vimentin, MMP9, and HIF-1 $\alpha$  to inhibit tumor metastasis. Meanwhile, the changes in the microbiota may also play an auxiliary role in improving the therapy response.<sup>67</sup>

In summary, microbiome-modulated nanomedicines provide multi-dimensional strategies for overcoming tumor immunosuppression and enhancing therapeutic effects through multiple mechanisms such as eliminating pathogenic

bacteria, regulating probiotics, reshaping the microenvironment, and synergistic treatment, which demonstrate broad prospects in cancer therapy.

## Conclusion and Outlook

The microbiome has been implicated as a critical factor in cancer progression. In the past few years, nanomedicines combined with microbiome modulation have become a promising novel paradigm in cancer therapy, especially for the CRC therapy. Compared to conventional therapies, this novel therapeutic approach offers several significant advantages. (1) Nanomaterials efficiently deliver drugs to tumor sites or specific microorganism-enriched regions through the enhanced permeability and retention effect or functional modifications, significantly increasing drug concentrations while markedly reducing systemic toxicity toward beneficial commensal bacteria and normal tissues.<sup>107,108</sup> (2) Synergistically deliver multiple functional molecules to achieve a synergistic effect of “microbiota regulation - immune activation - direct tumor killing”, which enhances the immune response through microbiota modulation, and effectively overcoming the drug resistance associated with traditional chemotherapy. (3) Exhibit improved penetration across biological barriers such as mucus and stromal matrices, importantly, reshape the TME and create favorable conditions for immune cell attack. (4) Personalized approaches involving nano-based prebiotics, probiotics, or antimicrobial strategies are expected to be designed to achieve precise “microbial editing” and advance precision medicine.

The rapid progress in this field benefits from deep interdisciplinary integration across various domains. (1) To achieve precise sensing, elimination, or modulation of specific microbes, corresponding targeted carriers are designed based on the characteristics of cancer-related microbes. (2) Intelligent responsive nanomedicines designed to be released in specific metabolite or enzyme environments, on the basis of the mechanism of microbiota effect on cancer therapy as indicated by multi-omics analysis. (3) Incorporate 16S rRNA sequencing or metagenomic analysis to evaluate the changes in the microbiota structure in animal models treated with nanomaterials is conducive to confirming the association between the microbial regulation induced by nanomaterials and the therapeutic effect of cancer.

Despite promising prospects, several challenges remain that require urgent resolution. (1) Off-target effects pose a substantial ecological risk, as non-selective antimicrobial activity may disrupt commensal communities and exacerbate dysbiosis. The spatial heterogeneity of intratumoral microbiota is poorly mapped, limiting rational design of targeted agents. (2) The response of individual to drugs is specifically influenced by the baseline microbiota,<sup>109</sup> the effect of nanomedicines in the microbiome modulation may vary from person to person. Whereas, high inter-individual variability in microbiome composition is often underappreciated, and most preclinical models fail to recapitulate human microbial diversity and host-microbe interactions. (3) Large-scale production, quality control, storage, and administration of engineered bacterial therapeutics present significant hurdles. The biosafety, long-term fate, and potential immunogenicity of engineered bacterial require more rigorous evaluation. (4) Most studies have not unequivocally established whether changes in the microbiota are a cause or a consequence of the treatment, the downstream specific signaling pathways and immune mechanisms demand more detailed investigation.

Based on current research advances and limitations, future efforts in clinical translation should focus on the development of smart responsive nanomedicines that release drugs in response to TME signals or microbial metabolites to achieve precise drug delivery. And carry out large-scale long-term toxicological studies, establish a complete safety evaluation system. Meanwhile, integrating systems biology and multi-omics technologies to characterize patient microbiome features for developing personalized nanomedicine strategies. In addition, it is necessary to deeply explore the downstream immune and metabolic mechanisms of nanomedicine therapy for cancer, providing new targets for combined therapy.

In conclusion, microbiome-modulated nanomedicines represent a vibrant and emerging interdisciplinary frontier. It is expected to unravel the complexity of the interaction between microorganisms and tumors through sustained collaborative efforts across nanotechnology, microbiology, and systems biology, and ultimately develop a novel highly effective and low-toxicity cancer therapies. This paper provides the first comprehensive review of fundamental advances in antitumor research from the perspective of nano-integrated microbial regulation. It systematically summarizes the advantages and limitations of this novel antitumor strategy, while proposing potential future directions in this field, thereby offering new insights for cancer therapeutics research.

## Abbreviations

BC, Breast cancer; BCSC, Breast cancer stem cells; BSA, Bovine serum protein; CRC, Colorectal cancer; CPT-11, Irinotecan hydrochloride; Cap, Capecitabine; DCA, Deoxycholic acid; DCs, Dendritic cells; DSBs, Double-strand breaks; EC, Esophageal cancer; ECM, Extracellular matrix; ETBF, Enterotoxigenic *Bacteroides fragilis*; ER, Estrogen receptor; FDA, Food and Drug Administration; FMT, Fecal microbiota transplantation; GC, Gastric cancer; HCC, Hepatocellular carcinoma; HER2, Human epidermal growth factor receptor 2; HIF-1 $\alpha$ , Hypoxia-inducible factor-1  $\alpha$ ; LipoDox, Liposomal doxorubicin; LPS, lipopolysaccharides; LR, *Limosilactobacillus reuteri*; LTA, Lipoteichoic acid; MMP-9, matrix metalloproteinase-9; MSNs, Mesoporous silica nanoparticles; NF- $\kappa$ B, Nuclear factor- $\kappa$ B; ORR, Objective response rate; OSCC, Oral squamous cell carcinoma; PC, Pancreatic cancer; PR, Progesterone receptor; PSC, Pancreatic stellate cells; REG, Regorafenib; ROS, Reactive oxygen species; SA, Salicylic acid; SCFAs, Short-chain fatty acids; TLR2, Toll-like receptor 2; TLR4, Toll-like receptor 4; TLR5, Toll-like receptor 5; TME, Tumor microenvironment; TNBC, Triple-negative breast cancers; THA, Thalidomide.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no conflicts of interest in this work.

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