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Novel strategies for modulating the gut microbiome for cancer therapy

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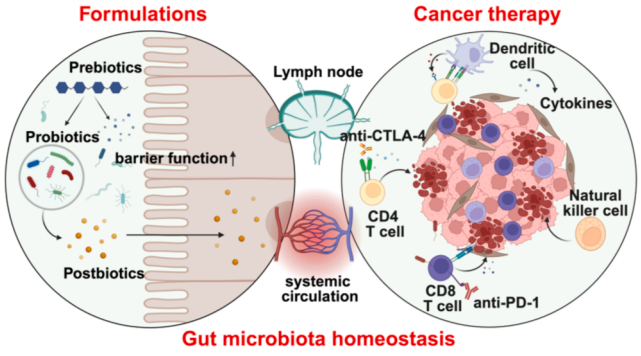
GRAPHICAL ABSTRACT



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ABSTRACT

Recent advancements in genomics, transcriptomics, and metabolomics have significantly advanced our understanding of the human gut microbiome and its impact on the efficacy and toxicity of anti-cancer therapeutics, including chemotherapy, immunotherapy, and radiotherapy. In particular, prebiotics, probiotics, and postbiotics are recognized for their unique properties in modulating the gut microbiota, maintaining the intestinal barrier, and regulating immune cells, thus emerging as new cancer treatment modalities. However, clinical translation of microbiome-based therapy is still in its early stages, facing challenges to overcome physicochemical and biological barriers of the gastrointestinal tract, enhance target-specific delivery, and improve drug bioavailability. This review aims to highlight the impact of prebiotics, probiotics, and postbiotics on the gut microbiome and their efficacy as cancer treatment modalities. Additionally, we summarize recent innovative engineering strategies designed to overcome challenges associated with oral administration of anti-cancer treatments. Moreover, we will explore the potential benefits of engineered gut microbiome-modulating approaches in ameliorating the side effects of immunotherapy and chemotherapy.

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1. Introduction

Human gastrointestinal tract (GIT) is the largest immunological reservoir that harbors 70 % lymphoid cells in the body and a diverse microbial community, including bacteria, viruses, and fungi [1,2]. These intestinal microorganisms play significant roles in modulating the local mucosal immune responses as well as systemic immunity through intricate cross-talks with immune and stromal cells in the gut [3,4]. Gut microbiome profile has been recently recognized as an important factor to affect the functions of the host immune system. For example, manipulating the gut microbiome has been shown to improve the outcomes of immune checkpoint inhibitors (ICIs) [5–7]. Several preclinical and clinical studies have revealed a set of bacterial taxa (e.g., *Bifidobacterium*, *Phascolarctobacterium*, *A. muciniphila*, and *Faecalibacterium prausnitzii*) that are associated with favorable clinical response to ICI treatment [8]. These beneficial bacterial taxa are recognized as probiotics, defined as "living microorganisms that provide health benefits to the host when administered in adequate amounts" per World Health Organization (WHO)/The Food and Agriculture Organization (FAO). Recent advances in genomics, transcriptomics and culturomics have accelerated the identification of various beneficial probiotics and better understanding of molecular mechanisms of action employed in modulating the host immune system [9]. In addition to probiotics, it is increasingly recognized that prebiotics and postbiotics can support the growth and activity of probiotics and provide defense against pathogens [10]. Specifically, prebiotics and postbiotics have been shown to improve the homeostasis of gut microbiota, maintain the gut barrier integrity, regulate innate and adaptive immune responses, and contribute to the complex and interconnected relationship between the gut microbiota and host immunity [11,12]. Clinical applications of prebiotics range from treatment of gastrointestinal diseases, allergic conditions, chronic metabolic diseases to mental illnesses [13,14]. Moreover, postbiotics have been documented to have potential health-promoting effects, including anti-inflammatory, anti-bacterial, anti-oxidant, anti-proliferative, and anti-tumorigenic activities [15,16]. Among postbiotics, short-chain fatty acids (SCFAs) have been mostly widely studied, and novel bioactive compounds derived from probiotic microorganisms' cell structure, lysate, or metabolites have been published [17].

Despite the promising advances in cancer immunotherapy for cancer treatment, intricate complexities exist, including heterogenous response to cancer immunotherapy and immune-related adverse events (irAEs) in cancer patients. Notably, irAEs are characterized by ICI-mediated activation of the immune system, leading to unintended autoimmune conditions (e.g., inflammation) in multiple organs/tissues (e.g. skin, intestine) [18]. The overall incidence of severe or life-threatening irAEs (grade $\geq$ 3) is as high as 55 % for cancer patients who received anti-cytotoxic T-lymphocyte-associated antigen 4 (α-CTLA-4) and anti-programmed cell death protein-1 (α-PD-1) combination therapy [19]. The clinical management of irAEs often involves the use of immunosuppressive agents (e.g., steroids). However, immunosuppressive agents can reduce the efficacy of ICIs. According to the clinical results from two US cancer centers, Arbour et al. showed that baseline corticosteroids during anti-programmed cell death ligand 1 (α-PD-L1) therapy were significantly associated with decreased progression-free survival and overall survival [20]. Moreover, long-term use of immunosuppressive agents may impair immune regulation and disrupt the homeostasis of gut microbiota, leading to an increased risk of infection and complications in immunocompromised patients [21,22]. Thus, there is intense research interest to understand the effects of immunosuppressive agents on the gut microbiota and how the gut microbiome affects the therapeutic efficacy and safety profiles of ICIs in patients [23]. For instance, an ongoing phase I clinical trial (NCT04038619) seeks to examine whether fecal microbiota transplantation (FMT) can mitigate ICI-associated diarrhea/colitis. Certain probiotics and postbiotics, such as *Bifidobacterium* and microbial tryptophan catabolite indole-3-carboxaldehyde, have been reported to treat ICI-associated mucositis or colitis without compromising the therapeutic efficacy of ICIs [18,24].

Human intestinal immune system is comprised of several components, including gut-associated lymphoid tissues (GALT) and gut-draining mesenteric lymph nodes (mLNs) as inductive sites for adaptive immune responses to antigens, and lamina propria as effector compartment [25]. To target and modulate the interface between intestinal microbiota and the host, oral delivery remains the most direct and preferable approach with high patient compliance [26]. Despite the clear benefits offered by oral administration approach, drug delivery to the GIT presents numerous physiological and physical obstacles. These obstacles include poor drug permeability across the mucosal layer and intestinal epithelium, microbial or enzymatic degradation, and harsh environments of GIT [27]. In fact, gut-targeted prebiotics and postbiotics must resist digestion and enzymatic degradation to reach GIT absorption to exert therapeutic efficacy. Moreover, intestinal retention of these therapeutics is also critical for maximizing their efficacy [28]. Other important factors include the physicochemical properties of drugs. As the majority of postbiotics are hydrophilic with small molecular weight, oral administration of these molecules generally exhibit poor bioavailability and pharmacokinetic profiles, thus limiting their overall therapeutic efficacy [29].

Engineering strategies have yielded a spectrum of drug delivery platforms poised to address multiple challenges associated with oral administration [30]. To maximize the efficacy of gut-targeted oral immunotherapy, engineered drug delivery systems, including polymeric, inorganic, and lipid-based biomaterials and extracellular vesicles, have been developed. Notably, engineered drug delivery systems have gained much attention for their capacity to shield therapeutic cargo from diverse biological barriers, realize targeted delivery, and increase the oral bioavailability and bioactivity of drugs (Fig. 1) [31–33]. Another noteworthy advantage of leveraging engineering strategies is the considerable versatility in manipulating materials at scales ranging from the nanoscale to the microscale, incorporating diverse functionalities [34].

This review primarily focuses on recent research on engineering strategies aimed at the oral delivery of prebiotics, probiotics, and postbiotics for cancer therapy. The emphasis is on exploring their potential in overcoming challenges associated with oral administration and modulating the gut microbiota in the setting of cancer therapeutics. Many clinical cancer treatment methods can lead to gut inflammation or autoimmune side effects. Thus, the review underscores recent efforts in managing autoimmune diseases and metabolic disorders, particularly gastrointestinal cancer-associated colitis. Table 1 shows representative clinical trials that aim to modulate the gut microbiota for cancer treatments.

This review article is intended to shed light on how these engineering approaches to modulating the gut microbiome might mitigate the side effects of chemotherapy or ICI therapy and potentially enhance the overall efficacy of cancer treatments. Ultimately, this review aims to stimulate innovative engineering principles and expedite their clinical application in the field of gut microbiome modulation and cancer therapy.

2. Prebiotics for improving the gut microbiome and anti-tumor immunity

In 2016, a panel of experts in microbiology, nutrition, and clinical research from International Scientific Association for Probiotics and Prebiotics (ISAPP) defined prebiotic as a substrate that can be selectively utilized by host microorganisms to confer health benefits. Prebiotics are typically generally recognized as safe (GRAS) substances [35], and the most well-known prebiotics are dietary polysaccharides, including resistant potato starch, inulin, fructo-oligosaccharides and galacto-oligosaccharides, and natural polyphenols [36]. While the exact mechanisms of action for prebiotics-based anti-tumor therapy are still being

studied for each prebiotic, in general, prebiotics are thought to exert anti-tumor efficacy by inducing the proliferation of beneficial microbes and leading to the production of microbial metabolites with anti-tumor properties. Recently, various engineering strategies have been applied to prebiotic formulations, aiming to prolong the intestinal retention of prebiotics, achieve controlled release of cargo at target sites, alter the biological interactions with commensal microbes (e.g., fermentation of dietary fibers or uptake by microbes), and improve their therapeutic efficacy against cancer [37].

2.1. Dietary polysaccharides

Dietary polysaccharides can modulate the gut microbiome and augment the anti-tumor effects of chemotherapy and immunotherapy. Currently, chemotherapy remains a primary therapeutic approach for various intestinal cancers. Upon oral administration, anti-tumor chemodrugs (such as 5-fluorouracil (5-FU)) exert their anti-tumor effect at the target tumor sites (e.g., colorectal cancer (CRC), pancreatic cancer). However, the physiological complexities of the gastrointestinal environments, including mucus layer, pH changes along the GIT, limited transit time through the intestine, and epithelial barriers, present challenges for efficient drug delivery to intestinal tumor sites. Clinical settings often require high doses or frequent administration of chemical drugs to achieve optimal therapeutic windows, leading to potential severe toxicity. Importantly, the gut microbiota has been recognized as a key regulator in the GIT to modulate the anti-tumor immune responses of chemical drugs. For example, Viaud et al. reported that cyclophosphamide could shift the composition of small intestinal microbiota and provoke the selective translocation of certain Gram-positive bacteria into the secondary lymphoid organs. Consequently, cyclophosphamide polarized $CD4^+$ T cells towards "pathogenic" T helper 17 (Th17) and Th1 cells, and gut microbiota played a key role in this phenotype conversion [38]. In addition, Ilda et al. reported that depletion of the gut microbiota with an antibiotic cocktail abrogated the anti-tumor efficacy of oxaliplatin [39]. These findings highlight the importance of the gut microbiota in chemotherapy and open the possibility of targeting the gut microbiota as a novel therapeutic approach during chemotherapy.

Dietary polysaccharides, complex macromolecules with high structural diversity, have been recognized for their ability to rapidly, reproducibly, and robustly alter the gut microbiota [40]. Many dietary polysaccharides are non-degradable by mammalian enzymes, but the gut commensal microbes can degrade these dietary polysaccharides, utilizing them as major carbon sources. Their microbial fermentation products, including SCFAs, provide energy for the gut commensal microbes and modulate their community simultaneously [41]. Besides, many polysaccharides possess certain biological functions, particularly in association with immune cells or under pathological conditions. Thus, dietary polysaccharides can be considered as bioactive compounds to modulate both gut microbiota and host immunity. This is particularly relevant in the setting of ICI-based cancer immunotherapy. ICIs have achieved great success in solid tumors in a small subset of cancer patients, whereas the majority of cancer patients failed to respond to ICIs including α-PD-1, α-PD-L1, and α-CTLA-4. This heterogenous response to ICIs among different populations is attributed to the intratumoral heterogeneity at the genetic and phenotypic level [42]. Recent studies have shown that gut microbiota can affect the host inflammation and immunity not only in the intestine *in situ* but also in the distant tissues systemically, and its modulation can promote the response rates to ICIs in the immunotherapy-refractory melanoma patients [43]. Among various microbiota modulation strategies, high dietary fiber diet (e.g., fruits and vegetables) has been shown to effectively improve the response to ICIs with high patient compliance [44]. In murine models, the introduction of pectin into the chow diet also improved the anti-tumor effect of ICIs [45]. The precise mechanism underpinning the relationship among polysaccharides, gut microbes and host immunity remains under investigation, but emerging evidence suggest that dietary

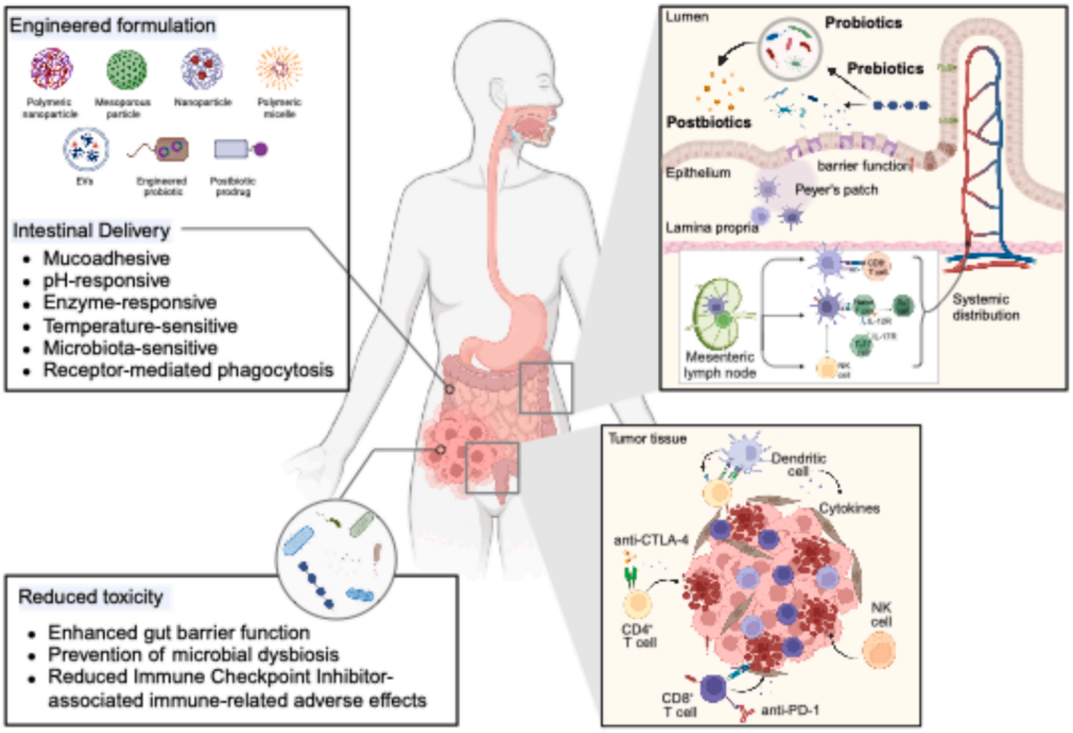

Fig. 1. Engineered drug delivery systems targeting the gut microbiota to enhance efficacy and reduce toxicity of cancer treatments. Various engineered formulations, including polymeric, inorganic, lipid-based biomaterials, and extracellular vesicles, serve as therapeutic platforms to overcome biological barriers and improve bioavailability of prebiotics, probiotics, and postbiotics for efficient intestinal delivery. These approaches can modulate of the intestinal innate immune system by activation or differentiation of antigen-presenting cells, $CD4^+$ T cells, $CD8^+$ T cells, or NK cells, restore gut microbial balance, promote anti-tumor efficacy of ICI therapies, and reduce toxicities associated with cancer treatments. This figure was created with BioRender.com.

Table 1
Representative clinical trials for gut microbiome modulation for cancer treatment.

References	Patients	Intervention	Phase	Recruitment Status
FMT				
NCT04038619	Genitourinary cancer patients with ICI-induced diarrhea or colitis	FMT	1	Recruiting
Dietary-derived Extracellular vesicles				
NCT01294072	Colorectal cancer patients	Curcumin conjugated with plant exosome tablet	1	Recruiting
NCT01668849	Head and neck cancer patients	Grape extract exosomes	1	Completed
Probiotics				
NCT03686202	Advanced solid tumor patients receiving ICIs	Microbial Ecosystem Therapeutic 4 (MET4), an orally delivered defined mixture of 30 intestinal bacterial isolated from the stool of a healthy donor	2/3	Active, not recruiting
NCT03072641	Colorectal cancer patients	*Bifidobacterium lactis* BI-04 and *Lactobacillus acidophilus* NCFM tablets	NA	Completed
NCT03358511	Breast cancer patients	Primal Defense Ultra multi-strain probiotic formula	NA	Completed
NCT03829111	Advanced renal cell carcinoma patients receiving ICIs	*Clostridium butyricum* CBM 588 probiotic strain	1	Active, not recruiting
NCT04589234	Metastatic pancreatic cancer patients	Attenuated strain of *Salmonella Typhimurium* expressing IL-2 + standard chemotherapy	2	Active, not recruiting
NCT04208958	Advanced or metastatic cancer patients	VE800, an oral live biotherapeutic consisting of 11 distinct commensal bacterial strains + Nivolumab	1/2	Completed

ICIs, immune checkpoint inhibitors; FMT, fecal microbiota transplantation; CRC, colorectal cancer; PFS, progression-free survival; spp, species.

fibers can enhance microbiota-derived stimulator of interferon genes (STING) agonists and secretion of type I interferon (IFN-I), thus modulating macrophage polarization and promoting the cross-talk between natural killer (NK) cells and dendritic cells (DCs) [45]. Despite the benefits of dietary fibers, the requirement for high daily consumption dose may reduce patient compliance. Along this line, emerging evidence suggest that an artificially high dose of a single polysaccharide additive (e.g., inulin, psyllium) can cause side effects, including liver cancer in dysbiotic mice [46], type-2 immune inflammation [47]. Therefore, it is desirable to engineer specific dietary fibers/polysaccharides into oral formulations that require reduced consumption doses, while maintaining their biological functions of modulating the gut microbiome.

In our previous work, we have developed a dietary inulin-based engineering strategy for *in situ* modulation of the gut microbiome, leading to improved systemic memory T cell responses and anti-tumor efficacy of ICIs. After *in vivo* screening of several candidates from FDA's list of GRAS including inulin, fructo-oligosaccharide, fucoidan, epigallocatechin gallate (EGCG, known as a polyphenol), and melatonin, we found that oral administration of inulin improved the systemic anti-tumor efficacy of α-PD-1 antibody. As polysaccharide gels with thickening effect can prolong gastric emptying, enhance adsorption to the intestinal mucous layer and extend the residence time [48], we engineered inulin into a gel formulation and demonstrated its colon-retentive properties, compared to native inulin solution [49]. Importantly, oral administration of inulin gel promoted the proliferation of 'beneficial' commensal microorganisms (e.g., *Akkermansia*) and triggered the release of microbial SCFAs. This in turn led to SCFA-mediated differentiation of $CD8^+$ T cells into stem-like memory $CD8^+$ T cells that synergized with α-PD-1 therapy (Fig. 2) [49], thus highlighting the potential of engineered prebiotics for improving cancer immunotherapy.

Prebiotic-based formulations can be developed for modulation of the gut microbiota in the setting of chemotherapy. For example, Hou et al. developed polylactic acid-polyethyleneimine (PLA-PEI) nanoparticles to encapsulate paclitaxel (PTX) [50]. These nanoparticles were further coated with prebiotics, hyaluronic acid-inulin (HA-IN), through charge interactions between PEI and HA. Inulin is resistance to degradation in the upper digestive tract, thus ensuring the delivery of nanoparticles to the colon. In the colon, the inulin shell is fermented by colon-specific bacteria, exposing HA to promote intestinal mucosal crossing and subsequent targeting of CD44 upregulated in tumor tissue. Besides, the proton sponge effect of PEI promotes the release of nanoparticles. The negatively charged nanoparticles exhibit increased cellular uptake by cancer cells *in vitro* and prolonged retention in tumor tissue *in vivo*, maximizing cancer cells' apoptosis, and therapeutic effect on orthotopic colon cancer compared to free drugs, partially through the recognition between exposed HA segment and CD44 on tumor cells. Further analyses of gut microbiota revealed that the nanoparticles increased the richness of the gut microbiota community structure, possibly due to the sufficient dose of HA-IN to substantially alter gut microbes [50]. In another example, Lang et al. reported an oral formulation composed of the prebiotic xylan-stearic acid conjugate to load capecitabine (Cap, the first-line chemotherapeutic agent for colorectal cancer) (SCXN), aimed to combine gut microbiota modulation and chemotherapy. Although the blood plasma half-life of Cap is very short (0.5–1 h), oral administration of SCXN clearly delayed Cap clearance from the systemic circulation, potentially due to its colon-retentive property [51]. On the other hand, SCXN also increased the abundance of beneficial *Akkermansia* and *Faecalibaculum*, concentration of microbial-derived SCFAs in the feces, and maintained the abundance of *Bifidobacterium*. As a result, SCXN improved the anti-tumor immunity compared with free Cap, doubling the median survival of tumor-bearing mice. These studies suggest the beneficial roles of prebiotic-based formulations for improving chemotherapy.

2.2. Dietary polyphenols

Dietary polyphenols are a diverse class of secondary plant metabolites found in green tea and red wine. The adsorption rate of polyphenols in the small intestine is low, and these unabsorbed polyphenols reach the colon, where commensal microbes further utilize them to release active microbial metabolites [52]. Consequently, dietary polyphenols can function as prebiotics, supporting or enhancing gut microbiota homeostasis and exhibiting health-promoting properties, including antioxidant, anti-tumor, and hypolipidemic effects. In the context of anti-tumor activity, Messaoudene et al. reported that oral supplementation of the natural polyphenol, castalagin (known as an ellagitannin), was capable of improving the intratumoral ratio of $CD8^+$/$FOXP3^+CD4^+$, modulating the gut microbiota with increased taurine-conjugated bile acids, and improving the anti-tumor activity and overcoming α-PD-1 resistance

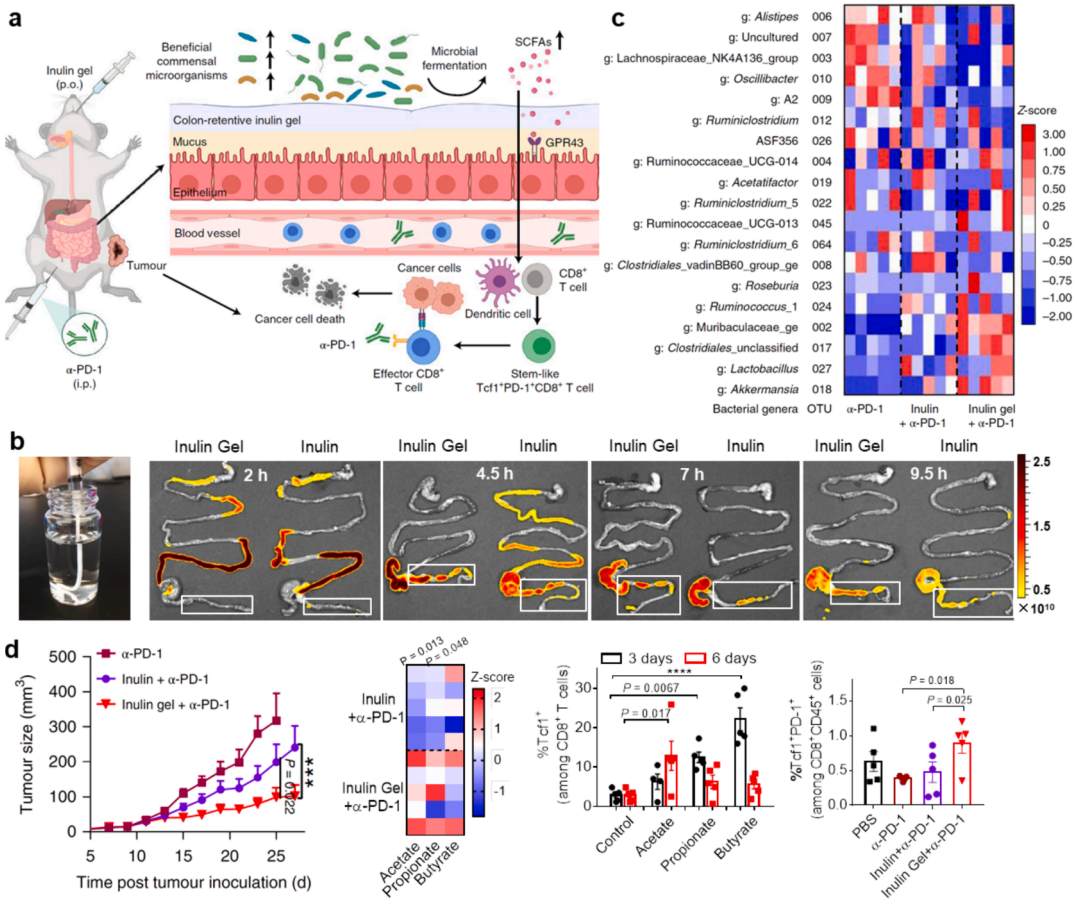

Fig. 2. Dietary polysaccharide-based oral formulation modulates gut microbiome and improves the efficacy of ICIs. (a), Schematic of inulin gel synergizes with ICIs antibody after oral administration. (b), Engineered injectable inulin gel and its "colon-retentive" behaviors in GIT. Inulin gel plus α-PD-1 altered the gut microbiota (c), and improved the anti-tumor efficacy (d), when compared with inulin plus α-PD-1. Mechanically, inulin gel plus α-PD-1 increased SCFAs in GIT, which promoted the frequency of Tcf1 on $CD8^+$ T cells *in vitro* and increased the $Tcf1^+PD\text{-}1^+CD8^+$ T cells in tumor.
Reproduced with permission from [49]

[53]. In another study, He et al. developed an oral tannin acid-armored tumor necrosis factor-α (TNF-α)-small interfering RNA delivery system. This system adhered to inflamed colon sites, modulated the gut microbiota-brain axis, and alleviated cognitive impairment, anxiety, and depression-like behaviors in colitis mice [54].

In addition to direct utilization in synergizing with other treatments, polyphenols have been widely employed to coordinate with metal ions (e.g. Fe^{3+}, Mn^{2+}) and form a metal polyphenol network [55,56]. This network can spontaneously form with pH sensitivity and act as coating materials to alter the physiological functional of probiotics [57]. Chen et al. developed a method for CRC treatment based on this metal polyphenol network. Specifically, therapeutic antibiotic metronidazole and 5-FU were loaded into mesoporous silica nanoparticles and decorated with a Fe^{3+}-EGCG network. These nanoparticles were dispersed in carboxymethyl cellulose (CMC) to form a mucoadhesive gel (AB-Gel). After colonic perfusion, AB-Gel could form a sticky layer on the surface of colonic mucosa with prolonged retention and modulate the CRC-associated gut microbiota. Meanwhile, AB-Gel released drugs in an acidity-controlled manner in tumor tissue due to the Fe^{3+}-EGCG network. The combined effect of antibacterial and anti-tumor effects of AB-Gel prevented the progression, metastasis and chemotherapy resistance of CRC [58].

Dietary polyphenols (e.g., EGCG or tannic acid) can be oxidized to form reactive quinones and can form multiple physical interactions with proteins [59]. This adhesive property of polyphenols has been used in improving dental bonding [60] and mucoadhesion in intestinal tract [61]. Lin et al. utilized the adhesive property of dietary polyphenols and engineered a temperature-sensitive, mucoadhesive hydrogel composed of EGCG and Poloxamer 407. This hydrogel exhibited a liquid state below body temperature. Upon rectal infusion into colon lumen, it turned into a viscous hydrogel. EGCG promoted its retention on the inflamed colonic mucosa and inhibited colitis-associated cancer induced by azoxymethane(AOM) and dextran sulfate sodium (DSS) [62].

2.3. *Dietary-derived extracellular vesicles*

Extracellular vesicles (EVs) are phospholipid bilayer-enclosed biological particles with size ranging from 30–150 nm [63]. EVs can be secreted by eukaryotic cells, plant cells and bacteria, and they contain various bioactive molecules, including nucleic acids, proteins, lipids and glycoconjugates [64]. Due to their small size and phospholipid bilayer structure, EVs can deliver molecular cargo and surface signaling molecules to recipient cells and alter the physiological processes, including immunogenic responses, inflammation, apoptosis, or gene/protein expressions, thereby facilitating communication among various cells. Recently, EVs derived from the diet have obtained increasing research interest, mainly due to their biocompatibility and bioavailability. Dietary-derived EVs can be absorbed by the intestinal tract and interact with commensal microbes, thus exerting physiological modulation functions.

Dietary-derived EVs can be sourced from plants (e.g., fruits and vegetables) or animals (e.g., milk and royal jelly). Dietary plant-derived EVs have different lipid compositions and cargos due to the variation in sources, influencing their internalization by commensal bacteria. Teng

et al. found that a higher level of phosphatidic acid in dietary plant-derived EVs improved their intestinal accumulation and uptake in *Lactobacillus rhamnosus*, while a higher level of phosphatidylcholine lipid promoted their migration from the intestine to the liver. The therapeutic cargo, RNAs, in these EVs can alter microbiome composition and host physiology [65]. Recent work further showed that rational design of lipid composition would enable the nanotherapeutics to precisely target specific organs [66], indicating plant-derived EVs may have broad applications in tissue/cell-targeted delivery. Interestingly, dietary-derived EVs from citrus lemon, broccoli, edible ginger, or grapes were all reported to achieve therapeutic efficacy in colitis or colitis-associated colon cancer models [67–70]. Mechanically, they can repair the intestinal barrier, promote the interactions or uptake in macrophages, or induce tolerogenic DCs via the activation of adenosine monophosphate-activated protein kinase, and reduce the pro-inflammatory cytokine secretion. For example, Zu et al. reported the EVs from tea leaf with desirable particle sizes (140 nm) can improve internalization by macrophages and accumulation in inflamed colon tissue due to the galactose group on EVs. Meanwhile, oral administration of these nanotherapeutics can prevent the inflammatory environment and restore the gut microbiota to a healthy status, thus alleviating colitis as well as colitis-associated colon cancer [71].

Milk is widely consumed and has crucial impact on children's growth and development. Du et al. reported that milk-derived EVs could effectively modulate the gut environment, increase the abundance of favorable microbes (e.g., *Akkermansia*, *Muribaculum* and *Turicibacter*), and decrease the abundance of "harmful" bacteria (e.g., *Desulfovibrio*). Milk-derived EVs altered the systemic lipid and amino acid metabolism and enriched the pathways of intestinal immune network for IgA production, retinol metabolism, and D-glutamine and D-glutamate metabolism in serum [72]. Badawy et al. observed that camel milk-derived EVs could modulate the gene expressions involved in oxidative stress, inflammation, angiogenesis, apoptosis, and metastasis in breast cancer and exert the therapeutic efficacy *in vivo* [73]. Despite the long history of milk consumption with its generally recognized safety profile, more investigations of dietary-derived EVs are warranted, especially in cancer patients. Samuel et al. reported controversial roles of milk-derived EVs in tumor control. They isolated bovine milk EVs that could survive from the harsh degrading conditions in the gut after oral administration. Intriguingly, they found that orally administered milk-derived EVs could reduce the primary tumor burden; however, these EVs accelerated metastasis in both breast and pancreatic tumor models. They also reported that oral intake of milk-derived EVs induced senescence and epithelial-to-mesenchymal transition in cancer cells [74]. Thus, controversial roles of milk-derived EVs in cancer treatments need to be further investigated.

Dietary-derived EVs showed great potential in gut microbiota modulation, drug delivery, cancer therapy, and other disease therapy, and there are multiple ongoing clinical trials examining their effects in cancer patients (e.g. NCT01294072, NCT01668849). A critical challenge limiting the clinical translation of dietary-derived EVs is in the absence of standardized isolation method, particularly for large-scale commercial productions.

3. Engineered probiotics for cancer therapy

The history of bacteria-based cancer therapy is traced back to the 19th century when Dr. William Coley used *S. pyogenes* and *B. prodigiosis* for cancer treatment [75]. To date, many bacterial genera have been identified as probiotics, defined as living microorganisms that, when administered in adequate amounts, confer a health benefit on the host [76]. Particularly in the field of cancer intervention, Tanoue and colleagues identified a consortium of 11 bacterial strains (VE800) from healthy human donor feces, which induced robust anti-cancer immunity [77]; corresponding clinical trials of VE800 and MET-4, another defined consortium, are ongoing for evaluating the efficacy of the bacteria consortium combined with ICIs for the treatment of different tumors (NCT04208958, NCT03686202). Commercially available probiotics have also been extensively involved in cancer preventions or combined with other therapies (NCT03072641, NCT03358511, NCT03829111), but the results have shown varied efficacy.

There are numerous challenges to overcome for probiotic-based approaches for successful gut microbiota modulation and cancer therapy. First, the harsh pH conditions, large amount of bile salts and digestive enzymes in the human GIT diminish the viability of orally supplemented probiotics. Bacteria-loaded capsules are therefore the most prevalent formulation for clinical trials. Alternatively, probiotics could be administered directly, which requires gastric acid neutralization before oral treatment [78]. Moreover, safety and efficacy are the limiting factors for the clinical applications of live probiotic-based strategies as their low therapeutic efficacy requires higher and more frequent doses, which may increase the risks of intestinal microbiota disruption and opportunistic infections [79]. Fortunately, due to advances in chemical engineering and innovations of gene circuits, probiotics could be genetically modified for oral therapies. On the other hand, nanotechnology has opened an avenue for cancer treatment as compelling drug delivery systems and theragnostic platforms, which can be incorporated with probiotics. Lastly, bacteria-derived components can be a surrogate to living bacteria for modulating gut microbiota and potentiating current cancer therapies.

3.1. Genetic engineering of probiotics

In the early stages, probiotics are usually identified from human/animal gut contents or fermented food products, such as *Lactobacillus rhamnosus GG* and *Escherichia coli Nissle* 1917 (EcN) [80]. Recent studies have discovered new probiotic strains and reported their efficacy in preventing colonic carcinogenesis and modulating gut microbiota and immune functions [81–83]. However, the potential toxicity restricts the clinical applications of these "primal" organisms, and genetic modifications have been investigated. For example, *PrfA*, the master virulence regulator gene was deleted in *Listeria monocytogenes* to be used as vector for tumor antigen vaccine [84,85], and a safer version, *Clostridiuym novyi* NT, was made by deleting a lethal exotoxin gene [86]. *Salmonella typhimurium* VNP20009 is a widely used attenuated strain with knockout of two virulent genes, *msbB* and *purl* [87]. Deletion of virulent genes introduced purine auxotrophy, allowing preferential colonization in the tumor microenvironment due to the high purine concentrations [88]. On the basis of VNP20009, HSC1 was developed by deleting *relA* and *spot*, which increased its anti-tumor efficacy while reducing systemic inflammation and liver toxicity [89]. A 10-fold increase in the maximum tolerated dose has been achieved by "cloaking" bacteria. Harimoto *et al.* engineered *Escherichia coli* Nissle 1917 (EcN), a widely studied probiotic bacterium [90], with a programmable capsular polysaccharide gene circuit. Transient expression capsular polysaccharides on EcN resulted in temporary evasion from the host immunity and harsh physiological conditions [91]. These studies suggest that genetical deletion of virulent genes or expression of inert coatings may improve the safety of bacterial therapy and may allow for orally administered probiotics for gut microbiota modulation and cancer therapy.

Colon-adhesive probiotics are considered more potent in combating pathogens [92,93] as adhesion to the intestinal mucosa plays essential roles in gut colonization [94]. Thus, genetic engineering has been exploited to target GIT components for probiotics delivery. For instance, Lr1064, an ABC-transporter component and member of the *Lral* family has been engineered to *Lactococcus lactis* MG1363 for mucus adherence [95], and the deletion of the polar flagellum on EcN promoted its mucus adhesion [95]. Ho et al. engineered *E. coli* that selectively binds to the heparin sulfate polysaccharides expressed on CRC cells by expressing histone-like protein A. In parallel, its binding released myrosinase which converted diet-derived glucosinolate into a potent anti-cancer agent sulforaphane. Oral administration of the engineered *E. coli* successfully

inhibited colitis-associated CRC [96]. In another study, *E. coli* was engineered to express synthetic adhesins fused to VHH and an N-terminal fragment of intimin from EHEC [97]. The VHH fragment enabled programmed adhesion to any target of interest. Besides, intimin β-domain and VHHs were resistant to proteases and denaturant agents [98], making it a promising approach for targeting the gut microbiome and providing probiotics-based cancer interventions.

In addition to tumor targeting motifs, probiotics have been engineered to express anti-cancer agents *in situ* for selective drug delivery and minimizing systemic toxicity for CRC. Orally administered Saltikva, an attenuated *Salmonella* containing human IL-2, was well tolerated and increased circulating NK cells and NKT cells in patients with metastatic gastrointestinal cancer [99]. The combination therapy of *Salmonella*-IL2 and FOLFIRINOX doubled the median survival of patients with metastatic stage 4 pancreatic cancer (NCT04589234). Din et al. designed an *E. Coli*-aCD47 nanobody delivery system with a synchronized lysis circuit. The synchronized lysis circuit carried the quorum sensing gene *luxI*, which was activated by reaching the population threshold; subsequent *ϕX174E* expression mediated bacteria lysis and nanobodies were released [100,101]. These studies have shown the great potential of genetically engineered probiotics to improve the pharmacokinetics and efficacy of current anti-cancer agents.

The quorum sensing circuit described above represents another intelligent genet editing strategy–that is, sense and respond mechanism. On the other hand, imbalanced gut microbiota and intestinal inflammation are one of the hallmarks of CRC [102,103]. Therefore, probiotics that can respond to environmental stimuli and address intestinal inflammation are beneficial for the intervention of gastrointestinal disorders and CRC through tuning the bacteria growth and controlled therapeutics expression [104]. Scott et al. constructed *Saccharomyces cerevisiae* yeast that can detect and neutralize the proinflammatory molecule extracellular ATP (eATP) in the gut by engineering human P2Y2 receptor (biosensor) mediated apyrase expression which degrades eATP. The self-tunable yeast probiotics suppressed the chemical-induced colitis and avoided the fibrosis and tissue damage triggered by excessive accumulation of eATP metabolites with the conventional constitutive expression system. In another case, pNanA was engineered to EcN as a genetic sensor for sialic acid, a biomarker for gut microbiome dysbiosis, which activates the secretion of bile salt hydrolase Cbh and therefore inhibits *C. difficile* infection by restoring the bile salt metabolism [105]. Similarly, EcN was engineered for tunable release of an immunomodulator AvCystatin that suppresses intestinal inflammation [106]. These results demonstrate the potential of self-modulatory and environment-responsive probiotics to exert therapeutic effects against CRC and GIT inflammation while limiting their side effects.

3.2. Engineer probiotics with biotechnology

Genetic engineering improves the safety and efficacy of probiotics as anti-cancer agents, and novel gene circuits are developed for intelligent delivery. In parallel, advances in nanotechnology offer an array of possibilities for drug delivery and multimodal theragnostics, seamlessly integrating into probiotics-based therapies. Polymeric materials, including alginate, k-carrageenan, xanthan gum, Eudragit, cellulose, and pectin, have been widely used for encapsulating bacteria to improve the storage stability and bacterial survival [107–112]. However, the microencapsulation approach, although shielding probiotics from chemical and physical assaults, may impede bacterial proliferation, intestinal recognition, and adhesion [113]. Therefore, innovative encapsulation methods are needed to ensure the optimal bioavailability of delivered probiotics.

In this regard, an interesting approach was reported for facile lipid coating of probiotics. EcN coated with dioleoylphosphatydic acid and cholesterol in calcium phosphate buffer was protected from extreme conditions in the GIT and extended intestinal retention without impairing bacteria growth [114]. Precisely controlled layer-by-layer techniques were introduced with tannic acid-Ca^{2+} complex and mucin [115] or chitosan/alginate through electrostatic interactions [116]. These approaches preserved the bacterial growth capabilities and improved mucus adhesion. They have been subsequently applied to coat engineered EcN for modulating the dysregulated gut microbiome in inflammatory bowel disease (IBD) [117]. Moreover, certain materials can selectively assist probiotic colonization by inhibiting commensal microbes from the host microbiota. For example, *Bacillus coagulans* encapsulated in calcium tungstate microgel inhibited the growth of the recalcitrant *Enterobacteriaceae* that occupies the ecological niche in DSS-induced colitis and enhanced the colonization of delivered probiotics [118]. Similarly, antimicrobial silver nanoparticles were loaded in a mucoadhesive hydrogel which inhibited the host microbiota and facilitated colonization *Peptostreptococcus*, whose abundance was correlated with prolonged survival in patients with oral squamous cell carcinoma. When combined with ICIs, probiotics plus silver nanoparticles exerted synergetic efficacy in a murine model of spontaneous oral squamous cell carcinoma [119].

Nanomaterials emerge as versatile tools, serving as functional substitutes for genetic engineering modules or adding attributes of nanomedicine to probiotics for improved therapeutic efficacy. While probiotics have been genetically edited to express tumor-associated antigens (TAAs) or anti-cancer therapeutics [120,121], their continuous expression can lead to high metabolic burden that may hamper bacteria growth and cause gene loss [104]. Therefore, instead of gene modification, TAA-loaded emulsion and self-assembled cationic nanoparticles with VEGFR2-encoding plasmid were conjugated to the surfaces of *E. coli* [122] or *Salmonella* [123]. Both bacteria-nanoparticle systems provoked strong T cell activation and suppressed tumor growth. Cao *et al.* took a different approach by modifying *Bifidobacterium longum* with an artificial antioxidant enzyme via boronic acid vicinal-diol-based click reaction [124]. *B. longum* directed the colon-targeted delivery of the artificial enzyme to scavenge reactive oxygen species (ROS), resulting in the remission of inflammation, promoting probiotic viability, and restoring the gut microbiota in chemically induced colitis in mice and dogs [125]. In another interesting study, Ma *et al.* designed a multi-modal biorobot, using a nanobody α-CD-47 expressing *E. coli* decorated with Fe_3O_4@lipid nanocomposites via the metabolic oligosaccharide engineering and click chemistry (Fig. 3). When administered orally, the biorobot accumulated in the orthotopic colon tumors under the guidance of alternating magnetic field. The nanocomposites converted magnetic signals into heat and triggered EcN lysis through a heat-sensitive promotor, releasing the therapeutic α-CD-47 nanobody *in situ*. The highly immunogenic bacteria lysate synergized with α-CD-47 and significantly suppressed the growth of colonic orthotopic tumor and elicited robust anti-cancer immune responses [126]. These studies exemplify the integration of genetic engineering strategies and multimodal treatment patterns of nanoparticles, showcasing the potential for improved targeted delivery and therapeutic efficacy.

3.3. Other bacterial components

Bacterial components have been utilized as alternatives to living bacteria for modulating the gut microbiota and potentiating cancer therapy due to better safety, ease in preparation, and stability. Compared to living probiotics, spores demonstrate greater shelf-stability and resistance to physiological stresses from the GIT [127,128], which is favorable for intestinal colonization and colon-targeted drug delivery. In a Phase 1b clinical trial, daily oral treatment with a consortium of *Firmicutes* spores (SER-287) [129] showed greater clinical remission and endoscopic improvement than placebo groups in ulcerative colitis patients. The oral treatment increased the α-diversity of spore-forming *Firmicutes* and decreased the abundance of pro-inflammatory species, such as *Klebsiella pneumoniae* and *Proteus mirabilis* [130,131]. Co-delivery of spores from *Clostridium butyricum* with dextran (spore-dex)

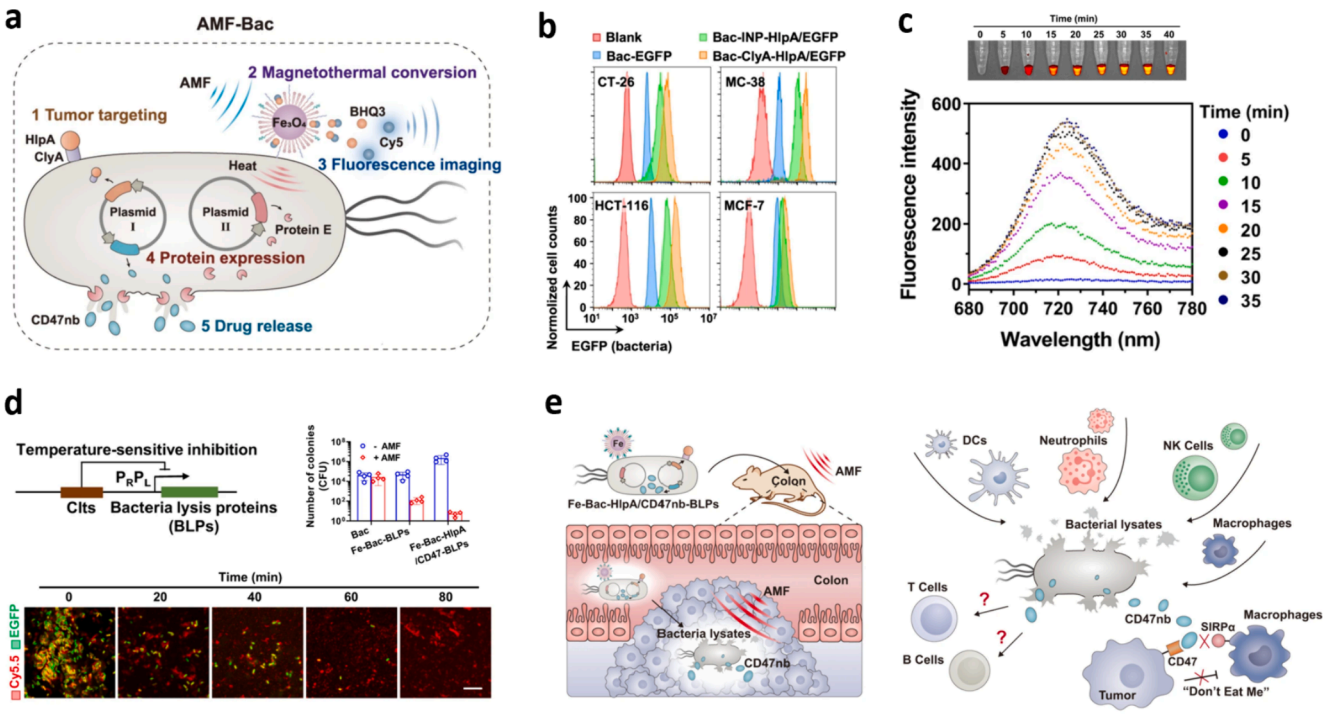

Fig. 3. Modular-designed engineered bacteria for precision tumor immunotherapy via spatiotemporal manipulation by magnetic field. (a), Design of the AMF-Bac with five functional modules. (b), The tumor-targeting ability of HlpA expressing bacteria. (c), Demonstration of the heat-induced fluorescence feedback. (d), Heat-induced bacteria lysis process. (e), Illustration of potential immune responses induced by AMF-Bac.
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improved selective spore accumulation at sites of colon cancer [132]. Meanwhile, spore-dex increased the gut microbiota richness, the levels of anti-cancer SCFAs levels, and the abundance of SCFA-producers *Eubacterium* and *Roseburia*. Combining dextran with chemotherapy drugs further inhibited the growth of spontaneous colonic neoplasms and orthotopic CT26 tumors. *Bacillus subtilis* spores encapsulated in cysteine-modified konjac glucomannan microspheres promoted spore intestinal retention and germination. This increased the oxygen consumption and generated a hypoxia milieu in the colon, which modulated the dysregulated gut microbial flora in multiple colitis models and inhibited the pathogenic *E. coli* triggered colonic tumorigenesis [133]. *C. butyricum* spores conjugated with gemcitabine-loaded mesoporous silicon nanoparticles enabled spontaneous pancreatic tumor migration through the "gut-pancreas axis translocation" and remarkably suppressed the growth of Panc-01 and Panc-02 tumors [134]. Another interesting strategy exploited the spore germination process to generate therapeutic nanoparticles in the gut. Researchers modified *Bacillus coagulans* spores with curcumin-folic or chemotherapy drug, deoxycholic acid [135,136]. The hydrophilic payloads self-assembled with disintegrated hydrophobic coat proteins and formed nanoparticles *in situ* during spore germination. They mediated subsequent cell uptake and penetration of epithelial cells. Those studies implicate spores as a feasible alternative to living bacteria, which can be dosed alone or combined with other therapeutic agents to modulate gut microbiota and treat different cancers.

Bacterial ghost (BG) refers to the non-living empty envelopes of Gram-negative bacteria, which is produced by the controlled expression of the lysis gene E that generates tunnels in the bacterial membranes and releases the cytoplasmic content [137]. BG shows good loading capacity [138], and its non-viable form renders BG an interesting synthetic drug delivery system [139,140]. Furthermore, BG preserves the adjuvant activity from pathogen-associated molecular patterns, making it a promising vaccine vector [141]. BG derived from EcN synergized with oxaliplatin for the treatment of CRC, prolonging mouse survival and leading to long-term memory effects against CT26 tumor through immunogenic cell death and activation of $CD335^{+}CD3^{+}$ natural killer T cells, $CD8^{+}CD25^{+}$ T cells, and MHC-II^{+} macrophages [137]. In another study, BG from *Lactobacillus acidophilus* was functionalized with prodigiosin, a bacterial second apoptotic metabolite, for the treatment of CRC. This bioinspired formulation showed good efficacy *in vitro* and has shown promise for CRC treatment due to the tropism of *Lactobacillus* to colon cells [139]. Manufacturing is the primary challenge for biomedical applications of BGs, where efficient gene-E mediated lysis relies on the logarithmic growth phase and is only applicable to gram-negative bacteria [142], while chemical methods can be extended to gram-positives but shows low efficiency [142,143]. Nonetheless, these studies show the potential of using bacterial ghost as immune adjuvant for the therapy of advanced CRC.

Minicells are anucleated nanoscale (100–400 nm) bacteria generated through abnormal cell divisions [144]. Different from the non-viable BG, minicells retain most cell functions and the cell components from the parent bacteria except chromosomes and thus cannot replicate [145]. Minicells have been investigated in cancer therapy for delivering shRNA or chemotherapy in animal models. Targeting motifs, folic acid and pHLIP, are engineered to increase tumor accumulation through ligand-receptor interactions or a pH responsive manner, respectively [146,147]. While these studies show minicells as a promising drug delivery platform for cancer treatment, the large-scale production can still be a limiting factor for their clinical translation [148].

4. Postbiotics for modulating the gut microbiome and host immunity

Recent investigations of postbiotics, known as metabolic byproducts from microbial fermentation or metabolic processes, have demonstrated immune-modulating capability and the potential to offer various benefits to host immunity, drawing parallels with probiotics and prebiotics [11]. In fact, increasing evidence also suggest that postbiotics can serve as a potential link among gut microbiota, various pathologies, and

systemic immune responses [149]. Furthermore, some of the recognized key features of postbiotics in immune modulation such as anti-inflammatory effects, immune cell regulation, and gut barrier function maintenance have positioned them as therapeutic intervention against various cancers or autoimmune diseases, underscoring them as promising tools for addressing adverse effects and complications of chemotherapy or immunotherapy [11,150]. In fact, these features linked to the host immune system's functionality have verified potential application of postbiotics as an adjuvant for cancer prevention and treatment, particularly for GI cancer. A few examples of widely studied postbiotics with biological activities are SCFAs, exopolysaccharides, cell wall fragments, enzymes, and other organic metabolites. As these components are emerging as novel immunotherapeutic agents, innovative engineering strategies have been introduced to extend their intestinal retention, improve pharmacokinetic profiles, and overcome GIT barriers to efficiently deliver postbiotics to the target sites in the GIT.

4.1. Short chain fatty acids

SCFAs, especially acetic acid, propionic acid, and butyric acid, are mainly produced in the colon through bacterial fermentation of dietary fibers and have been shown to play crucial roles in immune homeostasis and autoimmunity [151]. In addition to their important role as energy source for intestinal epithelial cells, their physiological effects have been widely explored in various indications, such as cancer, IBD, ulcerative colitis, diabetes, and atherosclerosis [151–155]. Moreover, recent studies have revealed SCFAs have diverse roles of either promoting the expansion of regulatory T cells (Tregs) or improving the function of effector T cells, largely depending on the therapeutic context as well as the immune context of specific diseases [156–158]. Despite their versatile therapeutic effects, poor pharmacokinetic profiles have been the bottleneck limiting their translational application. SCFAs with low molecular weight are readily cleared out from the systemic circulation, making it difficult to maintain their therapeutic drug concentrations. To overcome their unfavorable *in vivo* pharmacokinetic properties, a growing number of studies focus on formulating SCFAs for oral immunotherapy using various drug delivery platforms, such as liposome, nanoparticle, and prodrug. For instance, Shashni et al. developed enzymatically degradable amphiphilic block copolymer-conjugated SCFA prodrugs for enhanced internalization of SCFAs (propionic acid and butyric acid) into the systemic circulation to inhibit circulating melanoma cells and lung tumor [159]. Owing to amphiphilic characteristic of poly(ethylene glycol) and poly(vinyl ester) segments comprising the block copolymers, the polymers self-assembled into nanometer-sized micelle-like nanoparticles in an aqueous environment. After oral administration, ester linkage between SCFAs and polymers was degraded by endogenous intestinal mucosal enzymes to facilitate sustained release of SCFAs from the nanoparticles, possibly due to its core–shell type design. Further *in vivo* studies in melanoma model revealed nanoparticle's inhibitory effects on tumor growth and metastatic potential of melanoma tumor. Besides, the carrier-free prodrug engineering strategy was also explored by Cao et al. for the treatment of autoimmune arthritis and experimental autoimmune encephalomyelitis [160]. In this study, a butyrate prodrug (SerBut) was prepared through esterification of butyrate to L-serine, which is an amino acid known to cross the blood brain barrier (BBB) via L-type amino acid transporter-1. Utilizing amino acid transporters, SerBut showed increased accumulation in the central nervous system, including the spinal cord and brain. Furthermore, amino acid transporter mediated uptake of SertBut in intestinal epithelial cells contributed to the enhanced oral butyrate absorption and bioavailability of the prodrug. As a result, orally administered SerBut showed therapeutic potential in ameliorating the severity of rheumatoid arthritis and multiple sclerosis by reducing inflammatory responses and modulating immune cell population, particularly increasing peripheral Tregs in both disease settings. However, the authors did not examine the effects of prodrug on maintaining the gut microbial homeostasis and commensal bacteria or functions of BBB endothelial cells. Nevertheless, this study highlights the therapeutic potential of SCFA-amino acid prodrug strategy to exploit amino acid transporter for improving oral bioavailability and absorption.

High fat western diet and excessive use of antibiotics can shift the gut microbiota composition and increase susceptibility to intestinal inflammation, food allergies and other metabolic diseases. This shift is characterized by the overgrowth of pro-inflammatory *Proteobacteria* and depletion of beneficial bacteria, including SCFA-producing *Clostridia* [161,162]. Among various therapeutic interventions, normalizing SCFA levels has proven effective in promoting gut barrier integrity and modulating the microbiome by restoring microbial and mucosal homeostasis [163]. Recent advances in genomic analyses further enabled identification of bacterial strains with protective potential, and increasing evidence show that butyrate-producing bacteria, such as *Ruminococcus, Clostridium, Eubacterium,* and *Coprococcus*, are intricately involved in modulating intestinal immune homeostasis and alleviating inflammation [164,165].

Inflammatory responses can create an environment inducive for cancer occurrence. Specifically, ICIs-mediated sustained T cell activation can cause severe gut inflammatory responses (e.g., colitis) that are even life-threatening during or after treatment [166]. Hence, managing inflammatory responses is crucial in the context of cancer prevention and therapy. Emerging evidences suggest the importance of gut microbiota in the onset of colitis, and recent innovative researches in intestinal inflammation and autoimmune diseases shed light on the potential of utilizing oral administration of microbiome-targeted postbiotics for addressing ICI-associated irAEs in cancer patients. For the treatment of colitis in mice, butyrate releasing polymeric micelle system has been explored [167]. Butyrate was esterified to the backbone sidechain of hydrophobic block (*N*-(2-butanoyloxyethyl) methacrylamide; BMA), which was polymerized with either (*N*-(2-hydroxypropyl)methacrylamide; HPMA) or methacrylic acid (MAA) hydrophilic block to form neutral (NtL-ButM) or anionic (Neg-ButM) micelle, respectively. Each diblock polymeric micelle formulation was able to transit and release butyrate in the distal small intestine (NtL-ButM) and caecum/colon (Neg-ButM) after intragastric administration. Following disposition of butyrate in the lower GI track, butyrate micelle treatment restored the intestinal barrier integrity in the inflamed colon, thus enabling its application in alleviating colitis in the $CD45RB^{hi}$ T cell-transfer model. Also, fecal microbiome analysis in vancomycin-treated peanut allergic mice revealed that ButM micelle treatment significantly increased *Clostridium* cluster XIVa bacterial species which are known to produce butyrate and upregulate Tregs (Fig. 4) [168]. Although some of the engineering SCFAs delivery strategies discussed above were not applied for cancer therapy, the results clearly support the potential application of SCFAs in the regulation of gut inflammatory responses. These strategies should have great potential for the prevention or treatment of various cancer, especially CRC, due to the substantial microbiome- and immune-modulation capabilities of SCFAs.

4.2. Exopolysaccharides

Exopolysaccharides are complex extracellular carbohydrate polymers that are metabolic byproducts of various microorganisms, particularly by lactic acid bacteria, and are commonly found in extracellular matrix of biofilms [169]. Encompassing a wide range of polysaccharides, these biopolymers have exhibited health-promoting properties, including anti-tumor, antioxidant, anti-inflammatory, and antiviral effects [170]. Many studies focused on exopolysaccharides produced by lactic acid bacteria, such as *Lacticaseibacillus paracasei*, *Lactobacillus plantarum*, and *Lactobacillus paraplantarum* for their potential roles in promoting the growth of probiotics and modulating gut microbiota [171]. Xiao et al. investigated the effects of capsular polysaccharides and cell surface layer protein extracted from *L. paracasei* SNB, and found they altered the composition of gut microbiota by

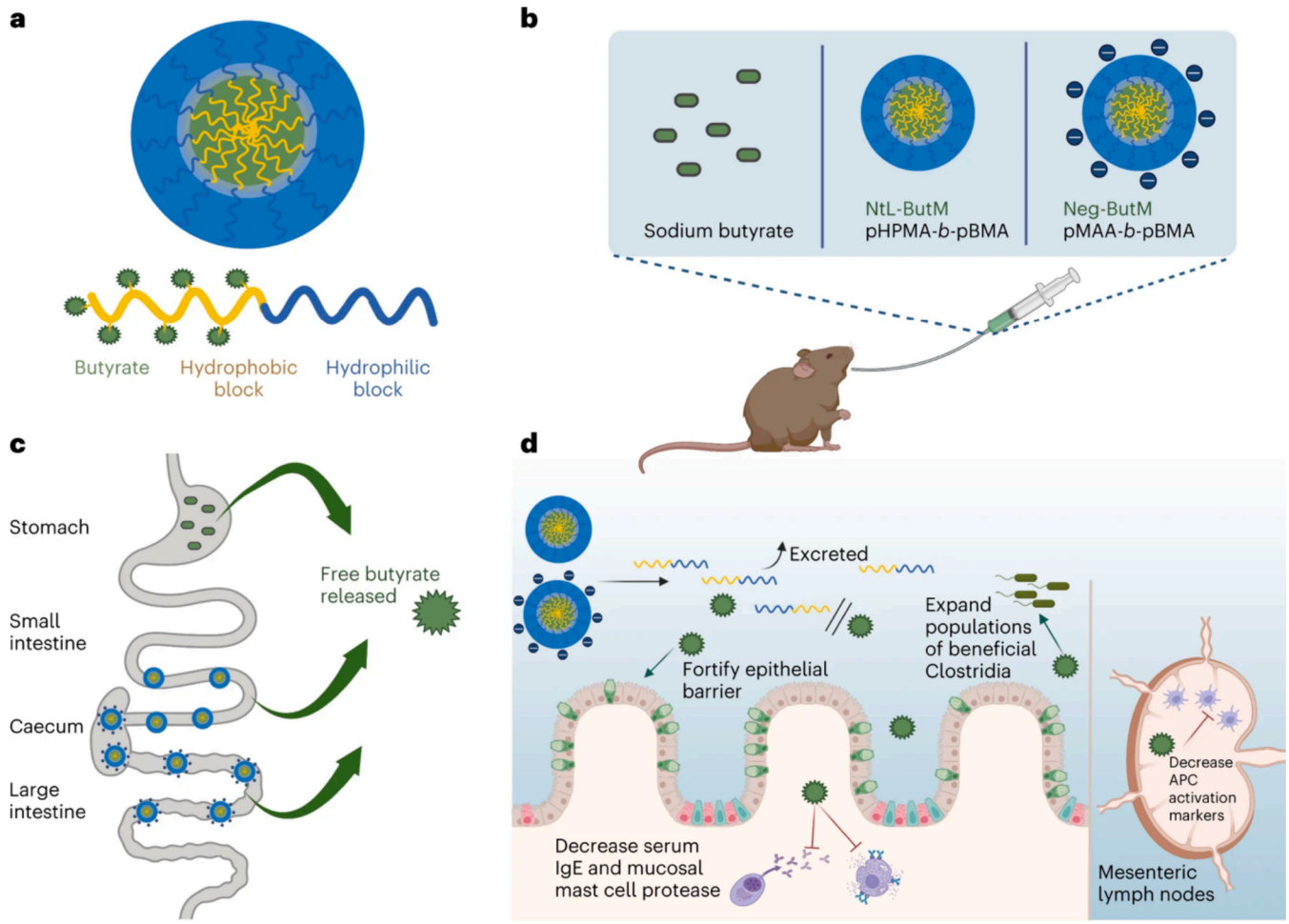

Fig. 4. Butyrate-conjugated polymeric micelles modulate gut microbiome and improve therapeutic efficacy against peanut allergy and T-cell-transfer model of colitis. (a), Design of butyrate releasing diblock polymeric micelle formulation. (b), Image of intragastric administration of neutral (NtL-ButM) or negatively charged (Neg-ButM) micelles containing butyrate. (c), Subsequent disposition of butyrate distal small intestine. (d), Distal GIT disposition of butyrate released from the micelle result in expansion of butyrate producing Clostridia bacterial species, upregulate Treg induction, decrease serum IgE and mucosal mast cell protease and downmodulation of activation and antigen presentation in autoimmune disease models.
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increasing the abundances of probiotic strains, including *Bacteriodes*, and *Bifidobacterium*, in *in vitro* fecal culture fermentation system [172]. Recent studies have highlighted the implications of abnormalities of the intestinal commensal bacteria and proliferation of specific bacterial pathogens or carcinogens (e.g., *H. pylori, E. coli, S. Enteritidis,* and *C. perfringens)* in the development of GI cancer, particularly CRC [102,173]. With unique characteristics of exopolysaccharides in terms of restoring the imbalance between the beneficial and opportunistic gut microbiota, exopolysaccharides hold promise as adjuvant therapeutics in cancer prevention and treatment.

4.3. Cell wall fragment extracts

A variety of cell wall components (e.g., peptidoglycan, teichoic acids, and lipopolysaccharide) derived from probiotic microorganisms have been investigated for inducing immune responses, particularly innate immune reactions [174]. These cell wall fragments can serve as microbe-associated molecular patterns to interact with specific pattern recognition receptors, mainly through toll-like receptors [175], thus modulating the host and gut microbial immunity. Weill et al. reported orally administered lipoteichoic acid (LTA) extracted from *Lactobacillus rhamnosus GG* increased the number of IgA^+ cells and activated DCs in mesenteric lymph nodes in chronically irradiated mice [176]. Although the relationship between the gut and the cutaneous immune systems needs further investigations, these findings suggest a potential role of LTA as an immunomodulatory messenger that can modulate the immune suppressive effect through the gut-skin axis.

Bacterial lipopopolysaccharide (LPS), a major component of the outer membrane of Gram-negative bacteria, has been largely studied for their immunomodulatory functions influencing a balance between host defense and tolerance to the resident microbial communities [177]. Unlike endotoxic LPS compounds, naturally occurring LPS from the mucosa-associated bacteria, *Bacteroides thetaiotaomicron* and *Prevotella intermedia*, has been studied as immune adjuvants which attributed to vaccine-mediated antigen-specific antibody titers when given together with an antigen [178]. Owing to its amphipathic property, LPS self-assembles into nanostructure, such as micelle [179]. Moreover, self-assembled LPS micelle could encapsulate different hydrophobic molecules (e.g., curcumin, doxorubicin, vemurafenib, and chloroquine), depending on the supramolecular assembly characteristics of LPS, size distribution, and critical micelle concentration of the micelle. In the context of CRC immunotherapy, immune-stimulating effects of bacterial LPS have been largely studied. Sulit et al. analyzed the link between immune characteristics and microbiome contributions in various CRC subtypes and identified that the immune-modulating effects of LPS were bacterial species-dependent [179]. *Fusobacterium periodonticum*-derived

LPS exhibited immune-stimulating effects based on the increased proinflammatory cytokine production in peripheral blood mononuclear cells (PBMCs), whereas *Bacteroides fragilis*- and *Porphyromonas asaccharolytica*-derived LPS showed immune-suppressive effects. This study underscored immunosuppressive potential of certain LPS in the CRC environment.

Bioinspired camouflage strategies utilize membranes derived from natural cells, such as erythrocytes, white blood cells, and cancer cells, as coating materials. These strategies have been investigated in various biomedical applications, including drug delivery, immune modulation, and detoxification [180,181]. Likewise, probiotics can benefit from the biomimicry approach in various scenarios. Erythrocyte membrane is an ideal bacteria cloak for intravenous administration owing to the well-known low immunogenicity and long-circulating properties [182]. Erythrocyte membrane encapsulation also lowered inflammatory activities, thus improving the safety of EcN and tumor colonization [183]. In another study, living EcN was camouflaged in extracted yeast membranes (YMs) by physical extrusion (EcN@YM) [184], which the β-glucan expressed on YMs facilitated Dectin-1 receptor-mediated phagocytosis by M cells and provoked strong mucosal immune responses. EcN@YM inhibited pathogenic bacteria, such as *Salmonella* and *Escherichia-Shigella*, and restored the gut barrier integrity. Conversely, bacterial membranes of different origins can be exploited to tailor the intestinal behaviors of nanodevices. EcN membrane facilitated the mucus binding of the diselenide-bridged mesoporous silica nanoparticles [185]. Probiotics-derived outer membrane vesicles provided shield to 5-fluorouracil loaded-mesoporous silica and reduced clearance by the mononuclear phagocyte system [186]. Nanoparticles coated by processed *Bacillus coagulans* spores improved *Bacillus* gut colonization and homeostasis and downregulated the abundance of bacteria related to the tumorigenesis of CRC. Notably, the spore derived nano-coating not only protected probiotics from environmental stress, but also provided nutrients for the exponential growth of *Bacillus* [187].

4.4. Enzymes and other metabolites

Microbial enzyme is a rapidly emerging field for its diverse applications as enzybiotics, digestive-aids, anti-inflammatory, metabolic-aids, and immune regulatory bioactive compounds [188]. Some are commonly associated with the metabolic activities of probiotics, primarily *Bacillus subtilis* and *Bacillus licheniformis*, which have the potential to produce lysozymes, fibrinolytic enzyme, and hydrolase [189]. Antioxidant enzymes, such as peroxide dismutase and catalase, are commonly produced by *Lactobacillus fermentum* and *Lactobacillus casei* [190]. With their ability to scavenge ROS and reactive species of nitrogen, these enzyme postbiotics have shown protective effects in CRC, Crohn's disease, and ulcerative colitis. However, it is challenging to deliver these microbial enzymes orally due to the harsh environment in the GIT. Thus, research groups developed nanoenzymes to exert the similar bioactivity as microbial enzymes. For example, Liu et al. discovered that platinum nanoparticles loaded in chitosan and alginate hydrogel can generate high levels of peroxide dismutase and catalase cascade catalytic activities as well as ROS-scavenging activities [191]. Oral administration of platinum nanoparticles showed protective effects against colitis induced by DSS, restoring the equilibrium of redox state. This nanoenzyme approach can be a promising alternative way to overcome difficulties of oral delivery of enzymes.

Apart from SCFA postbiotics, there has been an increasing number of reports on microbial metabolites that positively influence metabolism, immunity, and maintain gut homeostasis. Advances in next-generation sequencing technologies and metabolomics profiling have further contributed to identifying novel biologically active microbial metabolites [192]. Various microbial metabolites have been reported as key regulators of the intestinal barrier and pathogenesis of chronic inflammation in the GIT. Yang et al. developed oral microcapsule formulation to co-deliver indole-3-propionic acid (IPA) postbiotic and three prebiotics (alginate sodium, resistant starch, and chitosan) for the treatment of colitis [193]. Microfluidic electrospray method was employed to formulate microcapsules (IPA@MC) encapsulating IPA with alginate/resistant starch, which was further coated by chitosan. IPA@MC enhanced disposition of postbiotics and prebiotics to the lower GIT, thus exerting the protective effects against colitis via reshaping the gut microbiota. IPA@MC treatment significantly increased the microbial diversity and the relative abundances of SCFA-producing bacteria (e.g., *Faecalibacterium* and *Roseburia*) in colitis mice. This report demonstrated microfluidic-generated microcapsule as a potential delivery platform to co-deliver prebiotics and postbiotics to drive synergistic effect against colitis. Given that colitis is one of the most common irAEs for ICI therapy discontinuation, particularly with α-CTLA-4 therapy, combination of postbiotics and prebiotics can be a promising strategy to ameliorate immune-related colitis, enabling resumption of ICI therapies.

5. Gut microbiota modulation for reducing toxicity

The combination of multiple therapeutic interventions including aggressive surgery, chemotherapy, radiotherapy, vaccine and/or ICIs has emerged as the first-line treatment for multiple cancers. These treatments are expected to work synergistically to clear the massive local tumor, and a recent phase I trial has achieved great success even in pancreatic cancer through substantial T cells activation [194]. However, the combined treatments, especially with chemotherapy and radiotherapy, can lead to severe complications in the GIT, including nausea, diarrhea, vomiting, bleeding, infection, perforation, and even death [195]. Moreover, the gut microbiome can alter dramatically and results in microbial dysbiosis, which impacts local and systemic immune profiles and diminishes the therapeutic efficacy of ICIs or chemotherapeutics. To address these unfavorable effects on gut microbiota, Tian et al. developed an orally administered polymeric adsorbent, SPORA-SN9, to selectively reduce the toxicity of chemotherapeutics against the GIT. SPORA-SN9 contained sugammadex motif that can form host–guest interaction with some hydrophobic drugs, including the widely used doxorubicin and irinotecan. This supramolecular interaction mitigated the chemotherapy-induced GI mucositis, protected the physiological barrier of GI tissues, and prevented microbial dysbiosis, thus improving the therapeutic synergy effect between doxorubicin/irinotecan and α-PD-1 antibody [196]. Similar oral adsorbents have been developed to minimize the adverse effects of antibiotics and certain metabolites [197] in various diseases. For example, AB-2004 developed by Axial Therapeutic has been designed to adsorb certain substances produced by gut commensal microbes to reduce their entrance into the bloodstream and brain, with the goal of treating the Autism Spectrum Disorder in children [198]. The adsorbent strategy represents a new way to modulate the gut microbiota, but the adsorption mechanism largely depends on electrostatic interactions, hydrophobic interactions, or nonselective adsorption. The precision of the adsorption process and the long-term biosafety considerations necessitate further attention.

Radiotherapy is extensively used in cancer treatments, but it can damage healthy tissues, immune systems, and gut microbiota via the ionizing radiation-induced local and systemic toxicity. Minimizing radiation-induced intestinal injury is particularly crucial in the treatment of intestinal tumors, where the small intestine exhibits high radiation sensitivity. One strategy is to use radioprotector (e.g., amifostine) for the normal tissue; however, amifostine is injected intravenously, thus limiting its oral application in intestinal protection [199]. Zhang et al. reported the amifostine-loaded microalga Spirulina platensis oral delivery system to protect the small intestine during radiotherapy. This amifostine-loaded microalga Spirulina platensis oral formulation distributed among intestinal villi, underwent progressive degradation, and achieved comprehensive drug distribution/accumulation throughout the small intestine, thus showing effective protection to the small intestine, compared with free amifostine. Meanwhile, this oral formulation maintained gut microbiota homeostasis with long-term

safety and prolonged the mice survival while reserving the tumor regression ability (Fig. 5) [200]. In another study, Shi et al. engineered sulfhydryl crosslinked bacterial cellulose hydrogel loaded with *cis*-dichlorodiamineplatinum. This gel increased the X-ray-induced double-strand breaks, therefore improving the radio-sensitivity to intestinal tumor cells *in vitro*. Moreover, after oral administration *in vivo*, the gel exhibited potent anti-tumor efficacy and increased the ratio of *Bacteroidetes/Firmicutes*, which reduced the X-ray-irradiation-induced colitis [201].

ICI-based immunotherapy increases T cell activation and proliferation and compromise the immunosuppressive functions of Tregs, thereby boosting the chance of irAEs. The dose-limiting toxicity is highly prevalent especially when multiple ICI antibodies are used, as discussed in the Introduction section. While the precise mechanisms of ICI-induced irAEs are yet to be elucidated, dysregulated gut microbiota has been implicated with the degree of irAEs. For example, *Faecalibacterium*, *Clostridia*, and *Escherichia* have been reported to be positively associated with ICIs-induced colitis, whereas *Bacteroidetes* and *Bifidobacterium* were negatively associated with ICIs-induced colitis [202]. Notably, Halsey et al. recently reported that FMT could alter the gut microbiome and treat refractory colitis induced by ICIs [203]. FMT significantly increased the α-diversity as well as the relative abundances of beneficial *Collinsella* and *Bifidobacterium*. Interestingly, it has been difficult to study ICI-induced irAEs in preclinical models partially because symptoms of ICI-induced irAEs in animals are not very severe. Recently, new murine models of ICI-induced colitis have been reported, including a DSS-model of ICI-induced colitis and α-CTLA-4-induced colitis in mice harboring microbiota derived from wild-caught mice [204,205]. These studies will accelerate research and development of therapeutics targeted to modulate the gut microbiome for mitigate and reverse ICI-induced irAEs.

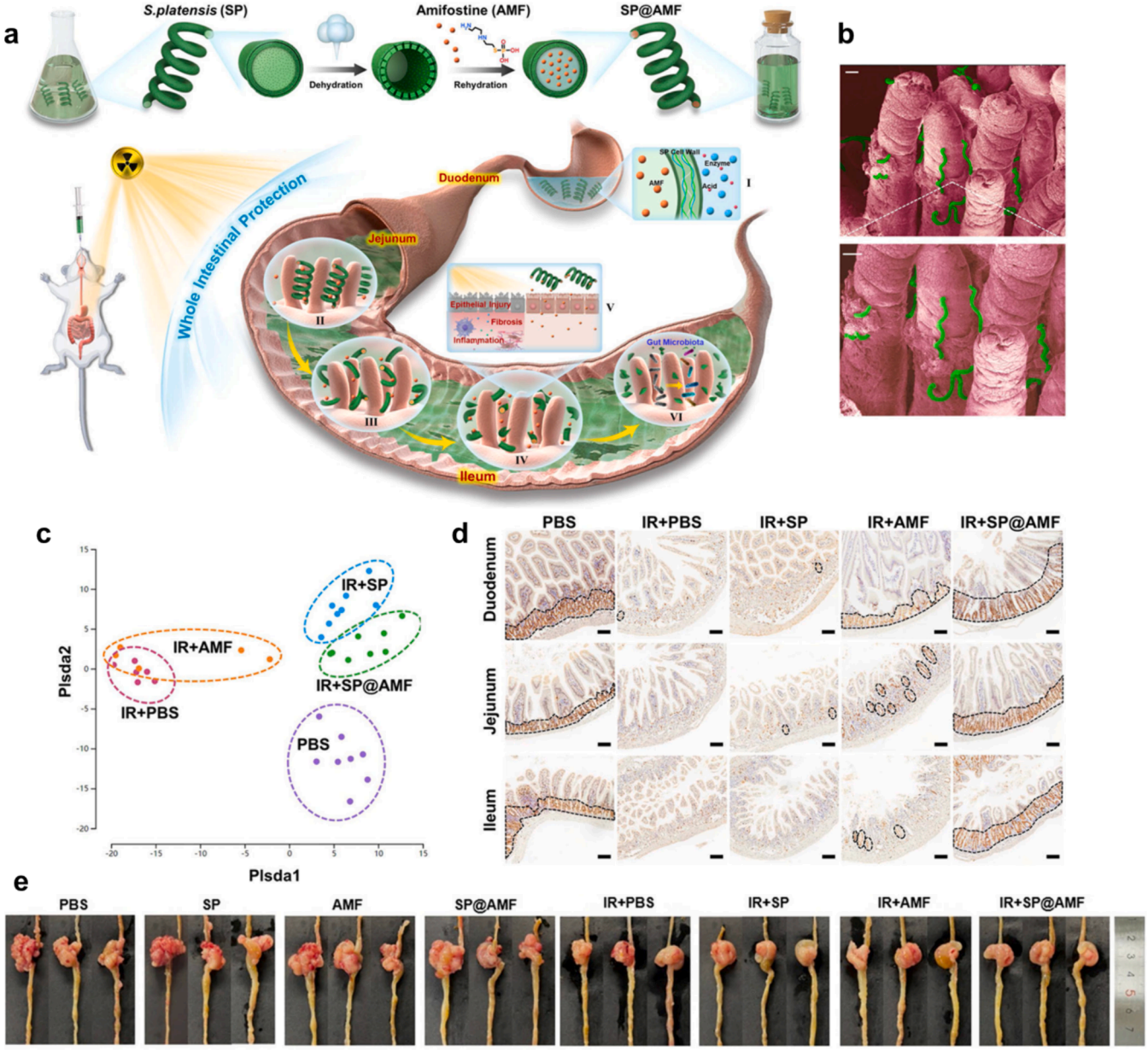

Fig. 5. (a), The schematic illustration of radioprotective mechanisms of SP@AMF. (b), SEM (pseudo-color) of SP@AMF between the intestinal villi. (c), SP@AMF-treated mice with radiotherapy exhibited similar microbial community structure to that of PBS-treated mice without radiotherapy. (d), SP@AMF protected the normal small intestine against radiotherapy-induced injury and (e), preserved the anti-tumor effect with regression of orthotopic colorectal tumor.
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6. Perspectives and conclusions

In summary, we have explored recent advancements in engineering strategies tailored to modulate the gut microbiome for cancer treatment. These engineered formulations play a pivotal role in delivering therapeutic cargos (such as RNA, drugs, metabolites), altering their biodistribution in the GIT, and fostering interactions with immune cells, commensal microbes, or enabling direct uptake by cells or microbes. Consequently, these formulations contribute to the modulation of immunophenotypes in cells, the relative abundances and metabolism of microbes, as well as the crosstalk between intestinal cells and gut microbes. Natural carriers, including polysaccharides, in these engineered formulations may also directly act as the fermentation/nutrition sources for the gut microbiome. Given that significant side effects associated with many current anti-cancer therapeutics, we have also discussed emerging strategies to maintain the gut microbiome homeostasis, while preserving therapeutic efficacy.

Despite the great success of engineering strategies for gut microbiome modulation and cancer therapy, this field remains in its early stage and faces various challenges: (1) Few gut microbiota modulation formulations are approved by FDA for clinical application in either cancer or other diseases therapy. Additional efforts are needed to ensure that the engineered formulations demonstrate biocompatibility, simplicity in structure and scalability in preparation, and robust and reproducible therapeutic efficacy *in vivo*, not only in the murine model but also in the larger animal model, such as primates. (2) Current engineering studies regarding gut microbiota focus on commensal bacteria, with limited exploration of the modulation of other microorganisms, including archaea, fungi, and viruses. (3) Many strategies as we discussed above employed hydrogel, receptor-ligand recognition to improve the intestinal retention of formulations. However, the prolonged retention behavior was just compared with their controls, the real retention times were usually limited to several hours due to the physiologic bowel movements, rapid turnover of mucus on the surface of epithelial cells, and the intestinal barrier. Sucralfate with sticky paste structure has been shown to coat on the intestine, but this coating behavior was transient [206]. Thus, achieving long-term retention in the GIT remains challenging and requires further investigation. (4) Another challenge is the precise modulation of gut microbiome. From FMT, macronutrient or prebiotics, antibiotics, a cocktail of bacterial species, a single defined bacterial isolate, and viruses that infect/kill selected microbe, to the microbial metabolite, these gut microbiome intervention strategies represent the approaches ranging from less precise to a more targeted manner [207]. However, the human gut microbiome exhibits significant interpersonal variation due to exogenous factors (e.g. household pet exposure) [208]. Moreover, it remains a challenge to modulate the gut microbiome precisely in the real world. Furthermore, the majority of current engineering strategies for gut microbiota modulation largely focus on analysis of fecal samples, thereby overlooking spatial variation along the GIT. Notably, a recent study highlighted that in some cases it was the small intestinal microbiota that affected the anti-tumor efficacy of therapeutic drug and participated in the phenotype conversion of immune cells [209]. To our knowledge, the modulation of small intestinal or colonic microbiome specifically has not been reported yet. (5) They are many questions need to be answered in this area. Microbial metabolites are widely believed to serve as the messengers between immune cells and microbes, while some study revealed that microbes could also be coated with mucus, then directly interact with DCs to affect the phenotype [38]. Besides, recent controversial studies have indicated that gut microbes may appear in distant tumor tissue [210,211]. Thus, certain microbial components may serve as antigens to initiate cross-reactive T cell response and could be employed as therapeutic targets [212,213]. However, mechanisms of bacterial translocation to the tumor tissues remain elusive, and therefore, it is unclear how immune cells interact with gut commensal microbes. Additionally, the interaction among immune cells, microbes and nervous system, the role of enzymes secreted by microbes or intestinal cells also call for more investigations. Answering these questions will enhance our understanding of the intestinal system and expedite the development of oral drug delivery formulations.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JJM declares financial interests as board membership, a paid consultant, research funding, and/or equity holder in EVOQ Therapeutics and Saros Therapeutics. The University of Michigan has a financial interest in EVOQ Therapeutics.

Data availability

No data was used for the research described in the article.

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