Journal of Advanced Research 64 (2024) 223–235

Contents lists available at ScienceDirect

Journal of Advanced Research

journal homepage: www.elsevier.com/locate/jare

Review Article

The role of gut microbiota and metabolites in cancer chemotherapy

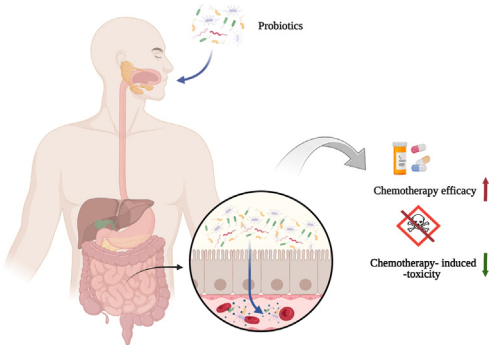
Shiyu Li [a], Shuangli Zhu [b], Jun Yu [a,*]

[a] Institute of Digestive Disease and Department of Medicine and Therapeutics, State Key Laboratory of Digestive Disease, Li Ka Shing Institute of Health Sciences, CUHK-Shenzhen research Institute, The Chinese University of Hong Kong, Hong Kong, China
[b] Department of Oncology, Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

HIGHLIGHTS

- We elaborate on the role of gut microbiota and microbial metabolites in the efficacy and adverse effects of chemotherapeutics.
- We further summarize the clinical potential of various ways to harness gut microbiota for cancer chemotherapy.
- The potential of gut microbiota severing as predictive markers for chemotherapy efficacy is discussed.
- Finally, we discuss current limitations and suggest potential approaches to facilitate utilization of gut microbiota in chemotherapy.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 3 August 2023
Revised 23 November 2023
Accepted 24 November 2023
Available online 26 November 2023

Keywords:
Gut microbiota
Cancer
Chemotherapy
Metabolites

ABSTRACT

Background: The microbiota inhabits the epithelial surfaces of hosts, which influences physiological functions from helping digest food and acquiring nutrition to regulate metabolism and shaping host immunity. With the deep insight into the microbiota, an increasing amount of research reveals that it is also involved in the initiation and progression of cancer. Intriguingly, gut microbiota can mediate the biotransformation of drugs, thereby altering their bioavailability, bioactivity, or toxicity.

Aim of Review: The review aims to elaborate on the role of gut microbiota and microbial metabolites in the efficacy and adverse effects of chemotherapeutics. Furthermore, we discuss the clinical potential of various ways to harness gut microbiota for cancer chemotherapy.

Key Scientific Concepts of Review: Recent evidence shows that gut microbiota modulates the efficacy and toxicity of chemotherapy agents, leading to diverse host responses to chemotherapy. Thereinto, targeting the microbiota to improve efficacy and diminish the toxicity of chemotherapeutic drugs may be a promising strategy in tumor treatment.

Abbreviations: 5-FU, 5- fluorouracil; AUC, area under the curve; CRC, colorectal cancer; DOX, doxorubicin; EcN, Escherichia coli Nissle 1917; FMD, fasting-mimicking diet; FMT, fecal microbiota transplantation; F. nucleatum, Fusobacterium nucleatum; GEM, gemcitabine; GI, gastrointestinal; IRT, irinotecan; KD, ketogenic diet; MTX, methotrexate; PTX, paclitaxel; SCFAs, short chain fatty acids; UroA, urolithin A.

* Corresponding author at: Institute of Digestive Disease and Department of Medicine and Therapeutics, State Key Laboratory of Digestive Disease, Li Ka Shing Institute of Health Sciences, CUHK-Shenzhen research Institute, The Chinese University of Hong Kong, Hong Kong, China.
E-mail address: junyu@cuhk.edu.hk (J. Yu).

https://doi.org/10.1016/j.jare.2023.11.027
2090-1232/

Contents

Introduction

There are around 3×10^{13} microbial cells inhabiting the epithelial surfaces forming the so-called human microbiota, which consists of bacteria, archaea, fungi, and viruses [1,2]. Furthermore, organs such as the breast, liver, and pancreas that were previously considered to be sterile, are now identified as potentially harboring low-biomass microbial populations [3]. The microorganism load varies from place to place. Approximately 97 % of microbial cells are bacteria in the colon and the rest are extra-colonic bacteria in the proximal gut, skin, lungs, *etc.*(2–3 %), as well as archaea and fungi (0.1–1 %) [4]. Such high density of colonic bacteria can help food digestion and acquire nutrition to regulate metabolism and shape host immunity. Therefore, the colon is deemed as the preferred site for microorganism study. With the development of revolutionary technology of high-throughput next-generation sequencing, metagenome and macrotranscriptome have brought microorganism research to a new peak. Current studies reveal the crosstalk between colorectal epithelial cells and gut microbiota, which is crucial to intestinal and even extraintestinal physiology, especially in regulating metabolism and shaping host immunity [5,6]. Remarkedly, the gut microbiota can impact tumorigenesis, progression, and metastasis of cancer, which has attracted much attention in recent years [3]. Although investigating the role of gut microbiota in cancer is just at the emerging stage, its influence on cancer therapy will show promising clinical potential in the coming era of precision medicine.

During the past decades, the mortality rate of cancer has dramatically decreased, to a great extent owing to the breakthrough of treatment, including improved surgical outcomes as well as increasingly efficacious multimodal chemotherapy and radiotherapy regimens [7,8]. Though exhibiting revolutionized outcomes, personalized therapeutic strategies like immunotherapy and targeted therapy face some formidable challenges, such as high costs and small number of benefited populations with specific biomarkers [9,10]. Thus, cytotoxic drugs are still the mainstay of treatment for the majority of advanced cancer patients due to the non-specific toxicity that presents in all cells with a high rate of replacement and division [11]. The application of chemotherapy is also limited by the severe systemic side effects and acquired drug resistance [12,13]. Nonetheless, the gut microbiota can mediate the biotransformation of drugs, thereby altering their bioavailability, bioactivity, or toxicity [14]. For instance, the chemopreventive effects of aspirin on colorectal cancer (CRC) tumorigenesis could be reduced under a high level of *Lysinibacillus sphaericus* in the gut due to its aspirin-degraded function [15]. With the concept of pharmacomicrobiomics, the importance of gut microbiota for drug modulation including chemotherapeutics has been gradually recognized [16]. Here, we review the evidence that the gut microbiota is implicated in the efficacy and adverse effects of chemotherapeutics (Fig. 1, Table 1). In addition, we discuss the clinical potential of harnessing gut microbiota for cancer chemotherapy.

Gut microbiota affects the efficacy of chemotherapy

Although manifold cytotoxic drugs have various mechanisms, they principally exhibit anti-tumor efficacy via targeting cell division and DNA integrity in the reproductive cancer cells [17]. Around 40 drugs are metabolized by gut microbes including methotrexate (MTX) and irinotecan (IRT), indicating that the gut microbiota can affect cancer response to chemotherapeutics [18]. Evidence showed an antibiotic cocktail reduced the therapeutic effect of oxaliplatin and 5-fluorouracil (5-FU) in CRC [19,20]. Notably, reactive oxygen species induced by commensal bacteria-dependent inflammatory response play a crucial role in maintaining the cytotoxicity of oxaliplatin [19]. In contract, some bacteria could promote chemotherapy resistance. For instance, *Fusobacterium nucleatum (F. nucleatum)* was related to CRC patients with recurrence post chemotherapy, and it lowered the efficacy of oxaliplatin and 5-FU. Mechanistically, *F. nucleatum* could induce autophagy activation to promote chemoresistance in a TLR4/MYD88-dependent manner [21]. In addition, Zhang *et al.* found *F. nucleatum* could also upregulate BIRC3 that directly inhibited the caspase cascade, leading to 5-FU resistance [22]. Intriguingly, fecal microbiota transplant (FMT) from healthy wild-type donor mice could restore gut microbiota composition and downregulate TLRs and MyD88 after chemotherapy [23], which indicated FMT has the potential to remodel intestinal microecology to overcome chemoresistance in CRC.

Apart from CRC, the gut microbiota is involved with extraintestinal cancers and probably contributes to paitent response to chemotherapy. Platinum-based chemotherapy drugs are widely used in cancer treatment, which exert a cytotoxic effect by binding to DNA thereby impairing DNA replication. Pflug *et al.* found gram-positive antibiotics decreased the efficacy of cisplatin in a clinical setting [24]. Another common chemotherapeutics gemcitabine

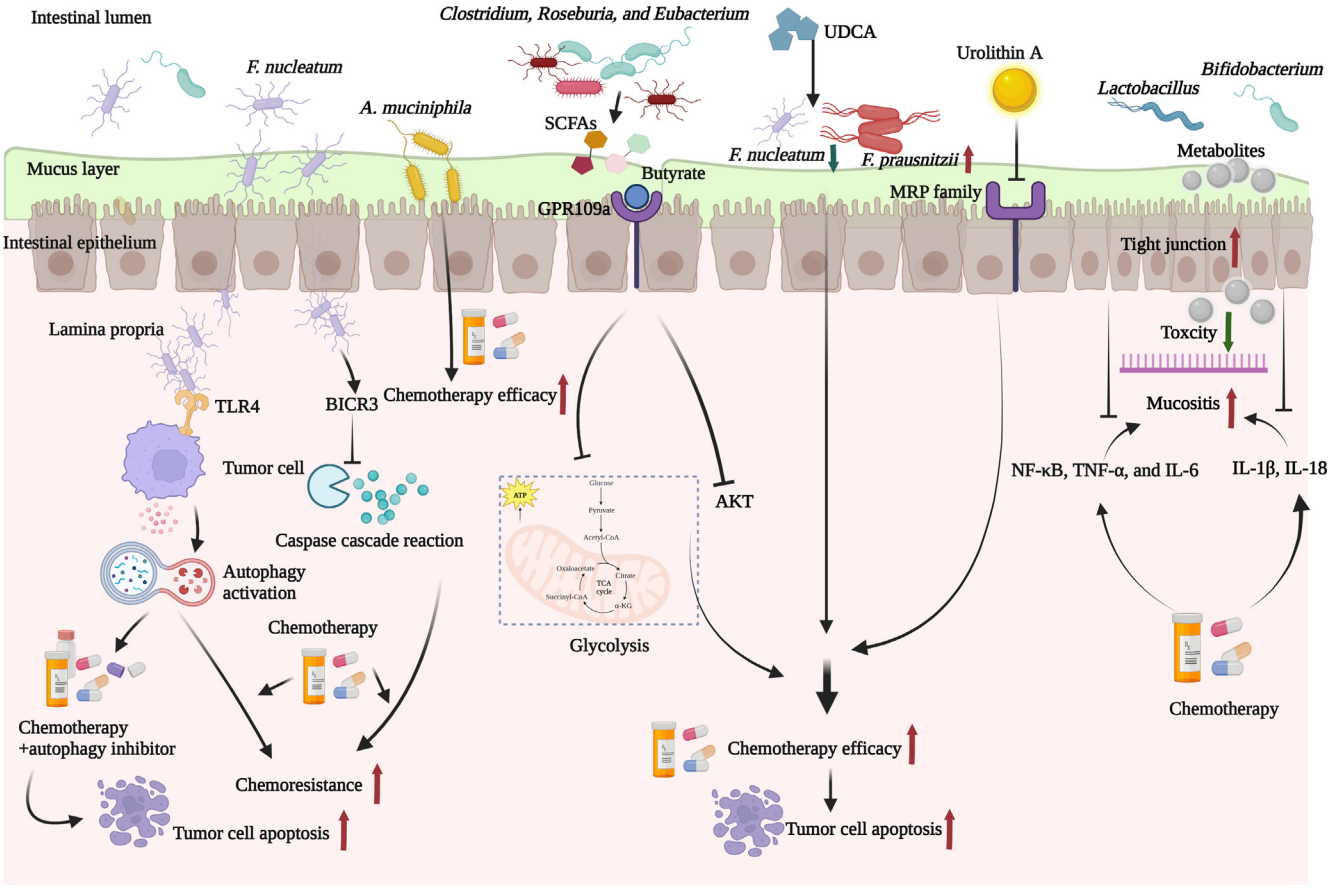


Fig. 1. The role of gut microbiota in cancer chemotherapy. Gut microbiota can directly affect chemotherapy efficacy. For example, *Fusobacterium nucleatum* can induce autophagy activation to promote chemoresistance in a TLR4/MYD88-dependent manner. *Fusobacterium nucleatum* can also upregulate BIRC3 that directly inhibits caspase cascade, leading to chemoresistance. *Akkermansia muciniphila* is favorable for enhancing chemotherapy efficacy. In addition, gut microbiota can produce metabolites like short chain fatty acids and ursodeoxycholic acid (UDCA) to improve chemotherapy efficacy. Butyrate can suppress glucose metabolism and target G-protein coupled receptor 109a-AKT signaling pathway to increase the chemotherapy efficacy, while UDCA reshapes the gut microbiota composition (increasing *Faecalibacterium prausnitzii,* and decreasing *Fusobacterium nucleatum*) to promote chemotherapy. Urolithin A promotes cytotoxicity in cancer cells via downregulating the expressions of drug transporters like the multidrug resistance-associated (MDR) protein family. Furthermore, Gut microbiota or microbial metabolites can reduce chemotherapy-induced toxicity including mucositis. For instance, *Bifidobacterium longum* can decrease the pro-inflammatory cytokines IL-1β and IL-18 and enhance the expressions of tight-junction proteins.

(GEM) is an antimetabolite, which is applied to pancreatic cancer, non-small cell lung cancer, breast cancer, *etc* [25]. The antitumor activity of GEM depends on its activation or degradation, where cytidine deaminase plays a pivotal role in the degradation process [26]. Growing evidence suggests bacteria can metabolize GEM into inactiveted form by deamination. It was demonstrated that *Gammaproteobacteria* and *Mycoplasma hyorhinis* could promote GEM resistance in pancreatic cancer and breast cancer, respectively [27,28]. Furthermore, the gut microbiota of breast cancer patients with chemotherapy response was enriched with *Clostridiales, Bifidobacteriaceae, Turicibacteraceae,* and *Prevotellaceae* [29]. Bawaneh *et al.* also found high abundance of *Akkermansia muciniphila* was favorable for enhancing the doxorubicin (DOX) efficacy in breast cancer [30].

On the other hand, chemotherapy can influence the composition of gut microbiota. After capecitabine plus oxaliplatin treatment, several changes were observed in the gut microbiota, like an increase in pathogenic bacteria and decrease in probiotics including *Dorea, Streptococcus, Roseburia, etc* [31]. Moreover, the abundance of *Firmicutes* was significantly reduced after chemotherapy [31,32]. Sougiannis *et al.* speculated *Firmicutes* could affect the efficacy of chemotherapy owing to its capability to produce short-chain fatty acids (SCFAs) [32]. Although increasing studies have reported alterations of gut microbiota after chemotherapy [33,34], whether these drug-induced microbial changes are directly related to chemotherapy response remain unclear. Thus, more efforts should be made to prove the role of these differential or chemotherapy-adapted bacteria in affecting the response to chemotherapy.

Gut microbiota reduces chemotherapy-induced toxicity

Gastrointestinal (GI) toxicity is a dose-limited side effect of manifold chemotherapeutics, which affects approximately 80 % of cancer patients [35]. Pathologically, chemotherapy-induced GI toxicity mainly refers to mucositis, resulting in infection and diarrhea [36]. Severe complications like bacteremia and sepsis not only lead to chemotherapy dose reduction, treatment cessation, and compromising remission but is also regarded as a major economic burden for cancer patients [36]. Currently, there are few effective medical measures to prevent and treat chemotherapy-induced GI toxicity.

In the last decade, preclinical and clinical research verified that chemotherapy could induce various changes in microbiome composition and diversity in the GI tract [32,37]. Importantly, the decrease of commensal bacteria can impair their protective effect against pathogenic colonization, thereby initiating a series of inflammatory pathways [38]. Thus, an alternative solution of ameliorating gut microbiota composition by probiotics supplement especially for *Lactobacillus*, was proposed for preventing or manag-

Table 1
Gut micriobiota and microbial metabolites affect the cancer chemotherapy.

Gut micriobiota	Chemotherapy	Disease	Effects Efficacy/ Toxicity	Mechanism	Reference
Fusobacterium nucleatum	OXA and 5-FU	CRC	↓/-	Inducing autophagy activation to promote chemoresistance in a TLR4/MYD88-dependent manner; Upregulating BIRC3 that directly inhibited caspase cascade	[21,22]
Gammaproteobacteria	GEM	PC	↓/-	Metabolizing GEM into inactive form by deamination	[27]
Mycoplasma hyorhinis	GEM	BRCA	↓/-	Metabolizing GEM into inactive form by deamination	[28]
Akkermansia muciniphila	DOX	BRCA	↑/-	NA	[30]
Lactobacillus	OXA and 5-FU	CRC	-/↓	Inhibiting inflammation by decreasing the expressions of NF-κB, TNF-α, and IL-6	[39–41]
Bifidobacterium longum	IRT	IRT-induced diarrhea	-/↓	Decreasing the pro-inflammatory cytokines IL-1β and IL-18	[45]
Probiotic Mixture Slab51®	PTX	PTX-induced neuropathy	-/↓	Modulating the serum proinflammatory cytokines concentration	[47]
Lactobacillus plantarum	5-FU	CRC	↑/-	Secreting metabolites to increase the expression of the butyrate transporter	[60]
Bacteroides vulgatus	5-FU	CRC	↑/-	Decreasing the abundance of *F. nucleatum*, and more efficient capacity of DNA repair	[79]
Microbial metabolites					
Butyrate	5-FU, docetaxel	CRC, lung cancer	↑/↓	Inhibiting glucose metabolism by GPR109a-AKT signaling pathway; Attenuating the inflammatory response and maintaining the integrity of intestinal mucosal tight junction, targeting glioma-associated oncogene homolog 1	[58,62,95]
Urolithin A	5-FU, PTX, and cisplatin	CRC	↑/-	Downregulating the expressions of drug transporters like multidrug resistance-associated protein family and ATP binding cassette family	[71,72]
UDCA	5-FU	CRC	↑/↓	Increasing the abundance of *Faecalibacterium prausnitzii* thereby enhancing the SCFAs level, and decreasing the abundance of *Fusobacterium nucleatum*	[76,77]
Nucleosides	5-FU	CRC	↑/-	Decreasing the abundance of *Fusobacterium nucleatum*, and more efficient capacity of DNA repair	[79]

Aberrations: 5-FU, 5- fluorouracil; BRCA, breast cancer; CRC, colorectal cancer; DOX, doxorubicin; NA, not acquired; PC, pancreatic cancer; GEM, gemcitabine; IRT, irinotecan; OXA, Oxaliplatin; PTX, paclitaxel.

ing chemotherapy-induced mucositis, and has achieved initial success in alleviating intestinal damage. In CRC, oral administration *Lactobacillus rhamnosus* or *Lactobacillus casei* variety *rhamnosus* could reduce the severity of diarrhea and intestinal mucositis induced by oxaliplatin and 5-FU via downregulating the expressions of NF-κB, TNF-α, and IL-6 [39,40]. *Lactobacillus* supplementation also prevented cisplatin-induced cardiotoxicity via inflammation inhibition [41]. According to clinical guidelines, IRT is the first-line chemotherapy for advanced CRC patients. Nevertheless, the primary limitation of IRT is its associated complication of diarrhea, especially late-onset diarrhea, which may result in significant dehydration, electrolyte imbalance, and nutritional deficiencies. IRT is transformed into its active form SN38, which is also regarded as the reason for late-onset diarrhea [42,43]. The key to reducing the side effects of IRT is to decrease the concentration of SN38 in the GI tract. A *meta*-analysis suggested that probiotics may be beneficial in preventing IRT-induced diarrhea, especially for grade $\geq$ 2 diarrhea [44]. For instance, selenium-enriched *Bifidobacterium longum* could be considered a promising therapeutic agent for IRT-induced diarrhea, as it could reduce the pro-inflammatory cytokines IL-1β and IL-18 and upregulate the expressions of tight-junction proteins occludin and ZO-1 [45].

In addition to intestinal toxicity, the gut microbiota is associated with chemotherapy-induced nerve injury. Peripheral neuropathic pain is often caused by paclitaxel (PTX) or platinum compounds. Neurons and glial cells are susceptible to chemotherapeutics-triggered inflammatory factors that are well-known starters of nociceptive pain in neuropathy [46]. Cuozzo *et al.* found that oral probiotic treatment can prevent PTX-induced neuropathy through increasing the expression of opioid and cannabinoid receptors in the spinal cord, reducing nerve fiber damage in the paws, and modulating the serum proinflammatory cytokines concentration [47]. Furthermore, a randomized controlled trial reported probiotics supplements could mitigate chemotherapy-related cognitive impairment by attenuating synapse injury, oxidative stress, and glial activation in the central nervous system [48].

It is noteworthy to pinpoint that antibiotics are frequently used for preventing chemotherapy-associated infection in clinic practice. Given the pivotal role of gut microbiota, whether the use of antibiotics for infection could generate other side effects such as neuropathic pain or diarrhea remains unknown. Thus, it is necessary to assess the pros and cons of antibiotics, and treatment strategies specifically targeting gut microbes should be considered.

Microbial metabolites in cancer chemotherapy

The gut microbiota synthesizes manifold metabolites or bioactive compounds, which play an important role in prompting normal physiology or diseases. These metabolites are generated from exogenous undigested dietary components and host or microorganisms-derived endogenous compounds via anaerobic fermentation [6]. They contain lipids, organic acids, amino acids, proteins, and peptides, *etc.* Microbial metabolic products can easily access the single layer of intestinal epithelial cells to interact with

host cells, and thus affect cancer pathogenesis, progression, and response to therapies [49].

SCFAs are one of the most common metabolites derived from the anaerobic fermentation of dietary fibers [50]. SCFAs are composed of acetate, propionate, and butyrate, and it is well-established that SCFAs principally exert extraordinary anti-tumor activity [51]. Acetate production pathways are widely distributed among bacterial groups, while pathways for propionate production appear more highly conserved and are distributed across relatively a few bacterial genera including *Lachnospiraceae* and *Ruminococcus* [52,53]. So far, butyrate is the most widely studied SCFA. Several clinical studies found the reduction of fecal butyrate level was correlated with colon tumorigenesis, which is mainly fermented by *Clostridium, Roseburia, and Eubacterium* [54,55]. Recently, the role of butyrate in cancer chemotherapy has been demonstrated. The level of butyrate was significantly higher in CRC chemotherapy responders, probably having potential as a predictor of chemotherapy response [56]. Moreover, butyrate may serve as a potential chemosensitizer. Increased glucose uptake and enhanced glycolysis have been identified as hallmarks of cancer cells, and thus suppression of glycolysis is regarded as an emerging and powerful approach to cancer treatment [57]. Butyrate could inhibit glucose metabolism to increase the efficacy of 5-FU in CRC via G-protein coupled receptor 109a-AKT signaling pathway [58]. Intriguingly, niacin could also activate G-protein coupled receptor 109a to suppress colonic inflammation and carcinogenesis, while whether niacin has the capacity to promote chemotherapy efficacy remains unknown [59]. Furthermore, *Lactobacillus plantaru*m-derived metabolites could increase the expression of sodium-coupled monocarboxylate transporter 1, a major butyrate transporter, thereby re-sensitizing CRC cells to 5-FU [60]. In pancreatic ductal adenocarcinoma, butyrate enhanced GEM-induced apoptosis of cancer cells and protected the integrity of intestinal mucosa by decreasing the abundance of pro-inflammatory microorganisms. Remarkably, butyrate could ameliorate some markers of kidney and liver damage caused by chemotherapy or cancer itself [61]. Similarly, butyrate and docetaxel additively inhibited the proliferation and promoted apoptosis in lung cancer via targeting glioma-associated oncogene homolog 1 [62]. These studies highlighted the predictive, therapeutic, and toxicity-reduced role of butyrate in cancer chemotherapy. Notably, there is an intriguing phenomenon that butyrate has opposing effects on the proliferation of normal versus cancerous colon cells, which is termed the butyrate paradox: butyrate facilitates the aberrant proliferation of colon epithelial cells at low concentration while suppressing cancerous colon cells at relatively high concentration [63]. Donohoe *et al.* found the Warburg effect may account for the butyrate paradox. In normal colon epithelial cells, butyrate functions as the primary fuel for cell metabolism, while in the cancer cells, glucose replaces butyrate as the major energy source owing to the Warburg effect. Thus, butyrate accumulates at a higher dose and functions as a histone deacetylases inhibitor, resulting in its anticancer properties [64]. Nevertheless, controversial findings on the role of butyrate in CRC still exist: butyrate could promote carcinogenesis even at a high concentration, making it difficult to explain the butyrate paradox simply by the difference in butyrate concentrations [65,66]. Such opposing conclusion emphasizes the importance of concentration and duration of butyrate administration in research, particularly in future clinical trials. In addition, several studies found other SCFAs except butyrate are also significantly differentiated between patients who received chemotherapy or not [56,67]. However, the role and mechanism of these SCFAs in chemotherapy are yet to be investigated.

Polyphenolic metabolites are other crucial products of the gut microbiota and have the capability to repair damaged DNA and inhibit colon pathogens [68]. Mechanistically, they can regulate DNA synthesis to inhibit the inflammatory cascade, and activate luminal detoxification enzymes to exert the anti-tumor function. However, only several bacterial species (e.g., *Bifidobacterium, Lactobacillus, Bacteroides, Eubacterium.*) that can catalyze the metabolism of phenolics have been identified so far with a huge interpersonal difference [69]. Urolithins metabolized from ellagic acid can suppress the proliferation and migration of tumor cells in multiple ways, including downregulating COX-2, matrix metalloproteinase-9, and the Wnt pathway [70]. There is increasing evidence to support the role of urolithin A (UroA) in chemotherapy. UroA increased the antitumor effects of PTX as well as cisplatin in esophageal carcinoma cells and 5-FU in CRC, respectively [71,72]. Mechanistically, UroA promoted cytotoxicity in cancer cells via downregulating the expressions of drug transporters like multidrug resistance-associated protein family and ATP binding cassette family [72,73].

Bile acids entering the colon undergo complex biotransformation performed by gut bacteria, resulting in the formation of secondary bile acids that can influence cancer chemotherapy [74]. Generally, ursodeoxycholic acid (UDCA) is one of the secondary bile acids with a tumor-suppressing role, which is supposed to exert chemotherapy-promoting function in recent years. Two key enzymes (7α-HSDH and 7β-HSDH) that are involved in the biosynthesis of UDCA are encoded by several intestinal bacteria such as *Clostridium, Eubacterium, Bacteroides, Escherichia coli, and Eggerthella lenta* [75]. Long-term UDCA treatment was related to an enrichment of *Faecalibacterium prausnitzii*, a bacterium known to mitigate 5-FU-induced mucositis [76,77]. In addition, UDCA treatment could decrease the abundance of *F. nucleatum* [76], which may enhance the chemotherapy efficacy indirectly. The gut microbiota represents a bridge between UDCA bioactivity and chemotherapy-promoting effects, while direct effect and mechanism of UDCA on cancer chemotherapy should be further explored.

Chemotherapy can eradicate cancer cells and control their proliferation by damaging their DNA. Thus, acquiring nucleotides for repairing damaged DNA may account for the occurrence of chemoresistance in tumor cells [78]. Recently, Teng *et al.* reported *Bacteroides vulgatus*-mediated nucleotide biosynthesis contributed the chemoresistance in CRC patients. Subsequent functional validation unveiled that exogenous supplementation of nucleosides or oral gavage of *B. vulgatus* increased the survival of CRC cells from 5-FU treatment via enhancing capacity of DNA repair [79].

Despite being a relatively new field, research about metabolites seems quite knockout. For instance, a growing number of metabolites have been identified to show outstanding efficacy against cancer in recent years, such as indole and indole-3-acetic acid, while deoxycholic acid and polyamines exert the opposite effect [51,80,81]. The research direction of metabolites has gradually changed from the charactierzation of overall metabolomic changes in patients to in-depth investigation on precise mechanisms of specific metabolites in cancer pathogenesis and therapies. Based on the current findings from basic research, clinical application of microbial metabolites in predicting chemotherapy efficacy and modulating response to chemotherapy is highly anticipated, yet more clinical trials with large cohort are still needed for verification.

Optimizing chemotherapy via the microbiota and metabolites

Given the significance of gut microbes and their metabolites in chemotherapy, more and more strategies for targeting the gut microbiota have been developed. Here, we summarize several ways to optimize chemotherapy through the modulation of microbiota and metabolites (Fig. 2, Table 2).

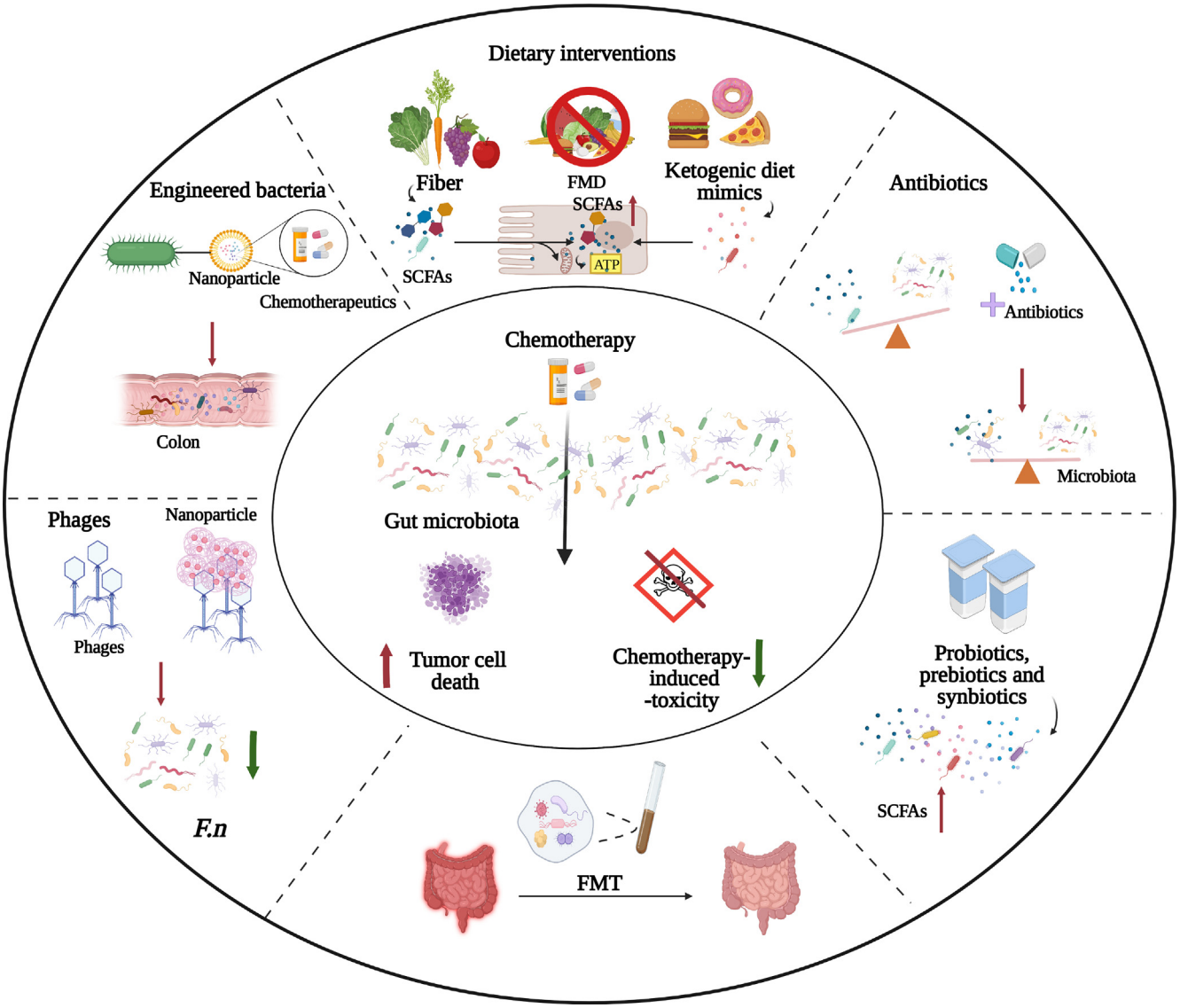


Fig. 2. The way to optimize chemotherapy via the microbiota and metabolites. Dietary interventions, targeted use of antibiotics, probiotics, prebiotics, synbiotics, FMT, engineered bacteria, and bacteriophages are the main strategies to harness gut microbiota for cancer chemotherapy. Dietary interventions: FMD, KD, and a diet rich in fiber can increase the level of SCFAs to enhance the efficiency and lower the toxicity of chemotherapy. Targeted use of antibiotics: antibiotics with a spectrum narrow enough to target a specific chemoresistance-associated bacterial species may induce favorable efficacy. Probiotics, prebiotics, and synbiotics: probiotics can release SCFAs (mainly), exopolysaccharides or other peculiar proteins to enhance the efficiency and lower the toxicity of chemotherapy. Prebiotics can increase the abundance of SCFAs-produced gut microbiota to optimize chemotherapy. FMT: FMT can mitigate chemotherapeutics-induced mucositis. Engineered bacteria: Bacteria can be modified to target tumor cells precisely, and even can be conjugated with nanocarriers loaded with chemotherapeutics to optimize chemotherapy. Bacteriophages: Phages can target a specific chemoresistance-associated bacterial species and can be also modified with chemotherapeutics-loaded nanocarriers to induce favorable chemotherapy efficacy.

Dietary intervention

An imbalanced diet may induce carcinogenesis, as it can alter the gut microbiota by skewing the abundance of specific species and metabolites [82]. For instance, western high-fat diet was correlated with CRC recurrence as well as the collagenolytic activity of *Enterococcus faecalis* and *Proteus mirabilis* [83]. Dietary fiber, fat and protein have relatively distinct but huge effects on microbiota composition and diversity. Short-term dietary interventions could reshape the gut microbiota, yet the changes could be revserved once returning to the original long-term diet [84]. Thus, dietary interventions are crucial for the development of CRC, and there has been much interests in investigating their effects in chemotherapy. It was reported that the Warburg effect promotes drug resistance via maintaining cancer stem cell status and facilitating epithelial-mesenchymal transition [85], emphasizing the importance of modulating energy metabolism through dietary intervention to overcome chemoresistance.

Numerous studies suggested that fasting or fasting-mimicking diet (FMD) before or during chemotherapy could reduce adverse effects and enhance the efficacy of chemotherapeutics [86]. Fasting or FMD therapies are supported by a crucial hypothesis that normal and tumor cells have distinct stress resistance. In general, normal cells downregulate proliferation-associated genes under starved condition, which impels them to turn into a self-sustained status and protect them from chemotherapy-induced toxicity, while tumor cells do not have such features [87]. Several microbes have been frequently found to be correlated with fasting interventions. *Faecalibacterium* including *F. prausnitzii* enrichment can produce abundant SCFAs, which contribute to chemotherapy efficacy. *Roseburia, Butyricoccus, Coprococcus,* and other genera with major SCFA producers, display similar patterns after fasting

Table 2
Optimizing chemotherapy via the microbiota and metabolites.

Methods	Microbiota composition alteration	Mechanism	Application	Reference
Diet interventions				
Fasting-mimicking diet	*Faecalibacterium, Roseburia, Butyricoccus,* and *Coprococcus* ↑	Reshaping the gut microbiota and increasing the production of SCFAs	Efficacy↑ and Toxicity↓	[88]
Ketogenic diet	*Akkermansia, Roseburia,* and *Ruminococcaceae* ↑, *Proteobacteria* ↓	Reshaping the gut microbiota and increasing the production of SCFAs	Efficacy↑ and Toxicity↓	[91]
High fiber diet	*Faecalibacterium, Roseburia,* and *Bifidobacterium*↑, *E. coli*↓	Reshaping the gut microbiota and increasing the production of SCFAs	Efficacy↑ and Toxicity↓	[94–96]
Probiotics, prebiotics, and synbiotics				
Probiotics (*L. plantarum S2, L. pentosus S3, L. rhamnosus 14E4*)	NA	Releasing butyrate, exopolysaccharides, and other peculiar proteins	Efficacy↑ and Toxicity↓	[98]
Flavonoids	*Bifidobacterium, Lactobacillus,* and *Roseburia*↑, *Escherichia-Shigella, Streptococcus* and *Enterococcus*↓	Increasing the abundance of probiotics and SCFAs, repairing the integrity of the intestinal barrier	Efficacy↑ and Toxicity↓	[106,107]
Dihydromyricetin	*Prevotella, Lactobacillus* and *Segmented filamentous*↑, *Fusobacterium*↓	Reshaping the gut microbiota and decreased the concentration of IL-17	Efficacy↑	[108]
Poria cocos polysaccharides	*Bacteroides acidifaciens, Bacteroides intestinihominis, Butyricicoccus pullicaecorum,* and *the genera Lactobacillus, Bifidobacterium, Eubacterium*↑, *Alistipes finegoldii, Alistipes massiliensis, and Alistipes putredinis* ↓	Modulating intestinal inflammation, improving the gut epithelial barrier	Toxicity↓	[110]
Targeted use of antibiotics	*Blautia*↓ (overuse of antibiotics)	Deceasing the concentration of SCFAs (overuse of antibiotics)	Efficacy↑	[115]
Fecal microbiota transplantation	*Lachnospiraceae and Roseburia*↑	Reshaping the gut microbiota	Toxicity↓	[126,127]
Engineered bacteria	NA	Delivering chemotherapeutics	Efficacy↑	[131–133]
Phage therapy	*Fusobacterium nucleatum*↓	Specifically targeting chemoresistance-associated bacteria and their biofilms	Efficacy↑	[137]

Aberrations: NA, not acquired; SCFAs. short chain fat acids.

[88]. Despite there has been indirect evidence showing that modulating the gut microbiota through fasting could affect the chemotherapy efficacy, fasting or FMD is indeed promising strategy as adjuvant of chemotherapy. However, considering almost all fasting-based interventions are difficult to adhere to for most people, FMD approach may have better compliance as patients can maintain their regular diet between cycles, or alternatively choosing complementary dietary approaches during the refeeding period. Remarkably, FMD does not lead to severe weight loss and show no detrimental effects on the immune and endocrine systems.

Ketogenic diet (KD) imitates the metabolic state of fasting through physiologically raising the level of ketone bodies. KD is a diet with high fat, adequate protein, and low carbohydrate, which exerts the function mainly by reducing the insulin level and generally does not lead to weight or micronutrient loss [89]. Zorn *et al.* found that KD reduced chemotherapy-induced toxicities and enhanced patient tolerance to chemotherapy [90]. The enrichment of *Akkermansia, Roseburia,* and *Ruminococcaceae* was observed in patients receiving KD, of which these bacteria are well-known SCFA producers and negatively correlated with CRC [91]. However, the mechanistic role of the microbiota in mediating anti-tumor effects or enhancing the chemotherapy efficacy of KD has so far not been investigated. Although KD showed promising results as a combined treatment, two phase I clinical trials both pinpointed that it remains a tough challenge on how to enhance the diet compliance of patients [92,93].

Considering the protective role of SCFAs in the GI tract, a diet rich in fiber such as Mediterranean diet has been brought to the forefront, which prompts the gut microbiota to generate more SCFAs [94]. Preclinical studies showed dietary fiber improved the efficacy and lowered the toxicity of IRT in CRC by increasing butyrate production [95]. Mediterranean diet could also increase the abundance of probiotics including *Roseburia*, *Bifidobacterium*, *Faecalibacterium, etc.*[96], highlighting that Mediterranean diet can maintain a favorable intestinal microecological environment even in cancer chemotherapy. Nonetheless, there are deficient clinical studies to further validate the efficacy, compliance, and safety of these nonpharmacological approaches.

Probiotics, prebiotics, and synbiotics

Probiotics are living microbes capable of conducing health benefits to the host with adequate intake [97]. Currently, the role of probiotics in enhancing chemotherapy efficacy is gaining an increasing amount of attention. Doublier *et al.* found three putative food-derived probiotics (*L. plantarum* S2, *L. pentosus* S3, *L. rhamnosus* 14E4) increase the effect of DOX in CRC cells by releasing butyrate, exopolysaccharides, and other peculiar proteins [98]. On the contrary, probiotic mixture supplementation failed to exert synergistic function with FOLFOX chemotherapy [99]. There is a perception that probiotics need to face acidic gastric juice, diverse digestive enzymes, and bile salts when going through the GI tract, accompanied by the changes of live microorganisms to unknown compounds, leading to the loss of some beneficial functions [100,101].

Prebiotics refer to substrates that are selectively utilized by host microorganisms to confer health benefits. The most common prebiotics include fructooligosaccharides, galactooligosaccharides, and inulin [102]. In addition to the anticancer effect, inulin and oligofructose significantly augmented the efficacy of six frequently used cytotoxic agents in cancer therapy without any supplementary risk [103,104]. Flavonoids are a group of polyphenolic compounds which occur widely in plants, and are substantial consumed in human diet [105]. The fruit of the date palm and *Astragalus mongholicus* Bunge-*Curcuma aromatica* Salisb contains significant amount of flavonoids that could significantly elevate the fecal contents of SCFAs and increase the abundance of probiotics, such as *Bifidobacterium*, *Lactobacillus,* and *Roseburia*, which may potentially enhance chemotherapy efficacy [106,107]. Dihydromyricetin, a natural flavonol, enhanced IRT efficacy by lowering the abundance of gut *Fusobacterium* [108]. Similarly, L-fucose ameliorated the pro-carcinogenic property of *F. nucleatum* in CRC, yet its synergistic effect with chemotherapy has not been clarified

[109]. Moreover, Poria cocos polysaccharides could improve therapeutic outcome of 5-FU in CRC by easing the cytotoxic effect of 5-FU and stimulating the growth of probiotic bacteria (e.g., *Bacteroides acidifaciens, Bacteroides intestinihominis, Butyricicoccus pullicaecorum, Lactobacillus, Bifidobacterium, Eubacterium*) [110]. Evidence showed that ginseng polysaccharides could reshape the gut microbiota with increased abundance of *Parabacteroides distasonis* and *Bacteroides vulgatus* to sensitize the response to PD-1 inhibitors [111]. Notably, although the importance of gut microbiota in mediating chemotherapy response has been emphasized, the specific role of each bacterial species plays still needs more investigation. In addition to being utilized by gut microbes to produce beneficial metabolites, prebiotics are deemed as a crucial component of some specific delivery systems to maintain stability, enhance efficacy, and reduce side effects of chemotherapeutics. For example, inulin and DOX conjugate were developed to improve cancer therapy with increased cytotoxicity, which could be attributed to stronger binding to DNA, easier access into cells, and larger molecular size to prevent efflux pumps from removing the conjugate from tumor cells [112].

Although synbiotics (a combination of prebiotics and probiotics) have not been investigated in potentiating chemotherapy efficacy, several randomized controlled trials demonstrated their potential for reducing adverse events in patients receiving neoadjuvant chemotherapy. Administration of synbiotics could lower the ratio of neutropenia, lymphopenia, diarrhea, and bacteremia in esophageal cancer patients during neoadjuvant chemotherapy [113,114]. Besides its synergistic effect, future research may focus on developing newer or personalized combination of synbiotics to target various cancer types that have different changes in the gut microbiota.

Targeted use of antibiotics

As aforementioned, broad-spectrum antibiotics have a detrimental effect on chemotherapy. Clinical studies revealed that overuse of antibiotics is related to poor prognosis in lung, liver, head and neck cancer patients who received chemotherapy [115–117]. However, Mohindroo *et al.* reported opposite results that the administration of antibiotics prolongs the overall survival and progression-free survival in pancreatic ductal adenocarcinoma [118]. It was speculated that the contrary outcome is attributed to the depletion of chemoresistance-associated bacteria. Ahmed *et al.* discovered that, whereas broad-spectrum antibiotics impair the efficacy of immune checkpoint inhibitors, narrow-spectrum antibiotics have no affects and even effectively reduce the incidence of side effects [119]. Thus, narrow-spectrum antibiotics that target specific chemoresistance-associated bacterial species may induce favorable efficacy. In addition, the duration of antibiotic administration is also critical. Using narrow-spectrum selective oral antibiotics one month or as soon as feasible before treatment could reduce disturbance to the gut microbiota and avoid unpleasant side effect and infection associated with surgery and other therapies [120]. Furthermore, chemotherapy can enhance the emergence of antibiotic-resistant pathogenic bacteria [121,122], and induce damage to the intestinal barrier, further aggravating infection due to microbial translocation to the bloodstream. Considering this issue, modifying enzyme inhibitors, membrane permeabilizers, and efflux pump inhibitors are now being used as remedies [120]. In general, antibiotic use is a double-edged sword. Under the premise of not affecting chemotherapy efficacy, how to optimize antibiotic use to prevent infection remains ambiguous and unresolved. Based on current findings, it is advocated for rational selection of narrow-spectrum antibiotics with early and appropriate use, as well as the use of appropriate antidotes to protect the intestinal barrier, suppress inflammation, and reduce colonization of harmful microorganisms, thereby facilitating CRC treatment with improved patient outcomes.

Fecal microbiota transplantation

FMT aims to treat diseases through microbiota alteration by transferring the completedly stable gut microbiota from healthy donors into the recipient patients to reestablish enteric dysbacteriosis and deal with symptoms [123]. Compared to probiotics, FMT transfers the whole microbial community rather than just a few species. Different from regular medicinal therapy, FMT usually only induces mild, transient, and self-limited gastrointestinal complaints. Nevertheless, two possible FMT-related deaths probably due to the inappropriate position of nasojejunal catheter, still concern the clinicians and patients [124]. Substitutionally, the FMT capsule seems to be more safe and feasible with no severe adverse effects or death [125]. To date, FMT has received FDA approval as a clinical treatment for recurrent *Clostridium difficile* infection, but its efficacy in chemotherapy modulation is yet to be tested. In preclinical research, Santana *et al.* and Wardill *et al.* found autologous FMT could significantly mitigate MTX- and 5-FU-induced mucositis, respectively, suggesting FMT may be critical in reducing chemotherapy-associated side effects through increasing the abundance of *Lachnospiraceae* and *Roseburia* [126,127]. However, there is deficient clinical evidence supporting the application of FMT in improving chemotherapy efficacy. Furthermore, identifying the critical microbial components among FMT materials that elicit chemotherapy responses is a key direction of FMT research. Due to its unclear influence on cancer survival, extensive clinical investigation is necessary prior to the wide application FMT as a strategy to impcfor cancer therapy [8,128].

Engineered bacteria

Efficient and safe drug delivery has always been a challenge in medicine. In most cases, chemotherapy fails to entirely eradicate tumor cells in a hypoxic microenvironment. Therefore, precise delivery of antitumor drugs or tumor suppressor genes to the anaerobic microenvironment in tumors via a targeted delivery system has been considered as one of the most clinically prospective cancer therapies with rapid development [129]. Although traditional synthetic nanocarriers can theoretically target tumor tissues, they have been gradually replaced by several biomaterials like exosomes or bacteria, due to their biotoxicity and poor biocompatibility [130]. *E. coli* Nissle 1917 (EcN) is one of the most commonly used bioengineered bacteria for drug delivery. Xie *et al.* constructed acid-lable EcN to conjugate with DOX based on the pH difference between tumor and normal tissues, which successfully enhanced the efficicency of drug absorption in tumor cells. Moreover, this conjugate could also lead to a higher DOX accumulation in tumors, compared to the commonly used nanocarriers [131]. In addition, Singh *et al.* developed nanoparticles containing 5-FU coated with prebiotics and probiotics, and such delivery system could allow 5-FU release only in the colon, thereby maintaining the integrity of gut microbiota simultaneously [132]. Intriguingly, *Clostridium butyricum* spores conjugated with GEM-loaded nanoparticles could migrate upstream into pancreatic tumors through the gut-pancreas axis, which increased threefold of intratumoral GEM accumulation compared to nanoparticles without *C. butyricum* spores conjugation [133].

Importantly, the colonization and growth of probiotics in the GI tract are often hampered because of the digestive processes. Therefore, it is urged to develop probiotic delivery system harboring improved mucoadhesive capability, enhanced intestinal colonization, high oral bioavailability, and superior resistance to the acidic gastric environment. The safety of engineered probiotics should

also be comprehensively assessed in clinical trials. The desirable cost-effectiveness and available technology for mass production should be taken into consideration. Novel oral delivery systems of probiotics via different mechanisms have been well summarized in other reviews [134].

Phage therapy

Phages are bacterial viruses widespread in the biosphere and able to modify or destroy bacteria [135]. A growing number of preclinical and clinical evidence has shown their therapeutic capability to tackle manifold infectious diseases, especially to target multidrug-resistant bacteria [136]. It is also a budding therapeutic approach for targeting the gut microbiota to overcome chemoresistance. For example, a novel dextran nanoparticle loaded with IRT could be linked to the phages that target *F. nucleatum* to augment the efficacy of IRT and simultaneously reduce side effects of the nanoparticle [137]. Bacteria attached to host cell surfaces are likely to enmesh into biofilms, which could play a crucial role in tumorigenesis and drug resistance. So far, no drugs can specifically target bacterial biofilms, while phages have shown potent ability to disrupt the structure of bacterial community in biofilms [138]. *F. nucleatum* could secrete amyloid-like adhesin to form biofilm and enhance its pathogenicity [139]. Additionally, compared with biofilm bacteria, the non-adherent ones tend to produce higher level of butyrate, indicating biofilm is able to influence host metabolism [140]. Thus, targeting biofilm by phages is a novel strategy to overcome bacteria-induced chemoresistance. Recently, Kabwe *et al.* identified a novel bacteriophage FNU1 that could disrupt *F. nucleatum* biofilm formation [141]. However, the lack of sophisticated regulatory framework and high-quality clinical trial data have restricted the development of phage therapy. Moreover, most clinical investigation on phage therapy in infectious diseases are accompanied by antibiotics use, thus the therapeutic and adverse effects of phage monotherapy remain unclear [136]. Given the detrimental effect of broad-spectrum antibiotics in cancer treatment, phage therapy that precisely target specific bacteria may have potential in reducing chemoresistance. Thus, it is ideal to define the core pathobionts that contribute to chemoresistance, thereby facilitating the development of an optimized cocktail of phages to eliminate these pathobionts. Nevertheless, more translational research is necessary before its clinical application, especially to evaluate the safety and efficacy of phage therapy.

Gut microbiota serves as predictive markers for chemotherapy efficacy

Given the crucial role of gut microbiota in cancer, enormous efforts have been invested to identify signature microbes for diagnosis and prognosis in patient stools, owing to the ease of collection, non-invasiveness, and repetability of fecal samples. Currently, numerous studies have investigated the diagnostic capability of gut microbiota in different cancer types [142–144], and some diagnostic models with microbial biomarkers for CRC could reach an area under the curve (AUC) of 0.96 [145]. Moreover, the signature of gut microbiota can also be applied to predict therapeutic outcomes such as immunotherapy and chemotherapy. "Random forest" is one of the most common methods in identifying microbial biomarkers and predicting chemotherapy response [146]. Li *et al.* identified a low abundance of *Roseburia faecis* predicted poor response to chemotherapy in GI cancer with an AUC of 0.818. Additionally, butyrate-producing bacteria such as *Roseburia* and *Dorea* were highly enriched in chemotherapy responders with robust predictive ability [56,147]. The gut microbiota also exhibits satisfactory predictive potential in other cancer types, including esophageal squamous cell carcinoma and breast cancer [148,149]. For instance, the abundance of *F. nucleatum* was related to poor response to chemotherapy in patients with esophageal squamous cell carcinoma [149]. As aforementioned, *F. nucleatum* can induce chemoresistance, hence targeting these pathogenic bacteria may yield potential to improve chemotherapy response.

Applications of gut microbiota to predict chemotherapy-associated toxicity have received attention recently. For instance, patients with lower bacterial diversity and a higher *Firmicutes*/*Bacteroidetes* ratio were likely to develop diarrhea after pelvic radiotherapy [150]. The gut microbiota could also predict the risk of immune-associated diarrhea in lung cancer patients [151]. However, no specific bacteria have been correlated with chemotherapy-induced toxicity, yet a study identified intestinal bacterial β-glucuronidase as a promising biomarker to predict IRT-induced diarrhea severity [152]. Targeting intestinal bacterial β-glucuronidase could reduce intestinal exposure to SN-38 and epithelial damage, meanwhile facilitating clinicians to identify appropriate patients to receive IRT treatment and allow accurate dosage adjustment. Of note, there is currently no approved intestinal β-glucuronidase inhibitor for clinical use [153]. Additionally, microbial metabolites such as butyrate can also reduce the toxicity induced by chemotherapeutics, with ideal diagnostic accuracy in CRC [154]. Hence, microbial metabolites may be potential biomarkers for predicting chemotherapy efficacy or chemotherapy-associated toxicity, after extensive clinical validation.

Future directions

The recent advance in microbial profiling technology has revolutionized our knowledge of the gut microbiota. As aforementioned, the gut microbiota is closely associated with chemotherapy response, and studies have demonstrated its clinical significance in predicting chemotherapy efficacy. However, to date there are still many unsolved issues. Apart from bacteria, human gut microbiota also comprises of other microbes including archaea, fungi, and viruses. Although enormous efforts have been invested on bacteria, the role of gut non-bacterial microbes is largely unknown. Unfortunately, due to their low abundance in comparison to bacteria, most genomes of these non-bacterial components are uncharacterized, which together form the so-called "dark matter" of the gut microbiota [155]. As a result, the function of these non-bacterial microbes in human health and disease remains elusive, not to mention to depict their role in chemotherapy. Recently, increasing research has been conducted to explore the alteration of these non-bacterial microbes in CRC [156,157]. With a more comprehensive picture of the gut microbiota, we would have deeper insights into gut microbes from different kingdoms, and their correlation with cancer chemotherapy.

Another unclear aspect is the spatial heterogeneity of gut microbiota. It is widely accepted that the composition of microbiota is distinct in different body regions [158]. A classic example is the microbial disparity between right-sided and left-sided CRC [159]. Moreover, microbes that are present inside the tumors were also found to be heterogenous [160], leading to differential interactions with host cells in the tumor microenvironment. In general, spatial heterogeneity in microbiota could lead to the inaccuracy of research, yet there is currently a lack of studies focusing on the variation of microbial community. More efforts are suggested to reveal the spital organization of microbial niches using novel technology, including multi-site sampling, single cancer cell-associated microbial profiling, or multiplexed spatial imaging [161]. In addition, intratumoral heterogeneity in host genetic background is known to induce chemotherapy resistance [162]. Mean-

while, whether microbial heterogeneity inside the tumors could impact chemotherapy response needs to be further investigated.

It is noteworthy to highlight that the composition of fecal microbiota was found to be distinct from that of the mucosal microbiota [163,164]. Therefore, it is unsatisfactory to use fecal microbiota to reflect the whole landscape of gut microbiota. Investigating the role and mechanism of the intratumoural microbiota in chemotherapy is also critical to demonstrate the relationship between gut microbiota and chemotherapy.

Conclusion and perspective

In the past few years, the research on gut microbiota has opened a new era for chemotherapy as well as other cancer treatments. There is accumulated evidence supporting the remarkable potential of targeting gut microbiota or microbial metabolites to enhance the safety and efficacy of chemotherapy, thereby improving survival of cancer patients. As such, increasing studies have begun to investigate approaches that directly modulate the gut microbiota as adjuvants of chemotherapeutics. However, given the wide spectrum of chemotherapy-related microbes reported among studies, it remains challenging to identify a universal and effective approach to modifying the gut microbiota in different patients. Additionally, the gut microbiota is highly susceptible to endogenous (e.g., host genetic background) and exogenous (e.g., environmental factors including diet, use of antibiotics, or even chemotherapeutic drugs) alterations. Further research should consider the interplay between microbiota and these host-related factors, thereby enhancing the efficacy of microbiota-targeting approaches that aim to enhance chemotherapy response.

For microbial metabolites, the quantitative contribution of metabolites should be considered prior to clinical application. Apart from metabolite fluxes, transit, absorption, and distribution of metabolites should also be premeditated. Although some metabolites like flavonoids have shown promising results in preclinical animal studies, they have poor bioavailability, making them hard to achieve optimal efficacy in human patients. Thus, how to enhance the bioavailability and efficacy of metabolites has been a tough challenge. To date, microemulsions, microencapsulation, and nano-delivery systems are proposed to improve the absorption of metabolites with poor bioavailability [105]. Notably, preclinical and clinical studies of long-term toxicity, pharmacokinetics, and molecular action of metabolites are still warranted, which are critical before their commercial application in the drug industry.

To date, most studies tend to provide a single snapshot of the gut microbiota before and after disease or treatment, as well as focusing on the function of a single bacteria. As a consequence, the dynamic changes in microbiota and intermicrobial perturbations during such a long course of treatment could be omitted. More longitudinal investigations are therefore recommended to fully uncover the microbial changes over the course of intervention. Another major problem is the disparity between clinical observations and clinical interventions stratifying the microbiota. Gut microbiota alteration may induce sepsis or immune dysfunction in patients, which could postpone the approval of microbiota-targeting therapeutic strategies to enter clinical trials. It is also noteworthy to pinpoint that current interventional studies are mostly performed in animal models, which could only partially mimic the human microbiota. Hence, the safety and efficiency of microbiota-targeting interventions must be ensured before their clinical applications.

In summary, although the field of therapeutic intervention through targeting gut microbes or microbial metabolites is still primitive, the resilience, stability, and sensitivity of gut microbiota have enabled researchers to utilize various microbial components as biomarkers or therapeutic targets. Approaches that modulate the gut microbiota are therefore very likely to become one of the next frontiers for precision and personalized medicine for cancer chemotherapy.

Funding.

This project was supported by Shenzhen-Hong Kong-Macao Science and Technology Program (Category C) Shenzhen (SGDX20210823103535016); RGC Research Impact Fund Hong Kong (R4032-21F).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

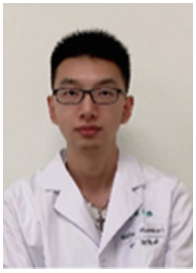
References

[1] Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. PLoS Biol 2016;14(8):e1002533.
[2] Zhai B, Ola M, Rolling T, Tosini NL, Joshowitz S, Littmann ER, et al. High-resolution mycobiota analysis reveals dynamic intestinal translocation preceding invasive candidiasis. Nat Med 2020;26(1):59–64.
[3] Cullin N, Azevedo Antunes C, Straussman R, Stein-Thoeringer CK, Elinav E. Microbiome and cancer. Cancer Cell 2021;39(10):1317–41.
[4] Sepich-Poore GD, Zitvogel L, Straussman R, Hasty J, Wargo JA, Knight R. The microbiome and human cancer. Science 2021;371(6536):eabc4552.
[5] Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. Nat Rev Microbiol 2021;19(1):55–71.
[6] Rooks MG, Garrett WS. Gut microbiota, metabolites and host immunity. Nat Rev Immunol 2016;16(6):341–52.
[7] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics. *CA Cancer J Clin* 2021;71(1):7–33.
[8] Alexander JL, Wilson ID, Teare J, Marchesi JR, Nicholson JK, Kinross JM. Gut microbiota modulation of chemotherapy efficacy and toxicity. Nat Rev Gastroenterol Hepatol 2017;14(6):356–65.
[9] Kantarjian HM, Fojo T, Mathisen M, Zwelling LA. Cancer drugs in the United States: Justum Pretium–the just price. J Clin Oncol 2013;31(28):3600–4.
[10] Huynh J, Patel K, Gong J, Cho M, Malla M, Parikh A, et al. Immunotherapy in Gastroesophageal Cancers: Current evidence and ongoing trials. Curr Treat Options Oncol 2021;22(11):100.
[11] Wu W, Pu Y, Shi J. Nanomedicine-enabled chemotherapy-based synergetic cancer treatments. J Nanobiotechnology 2022;20(1):4.
[12] Knezevic CE, Clarke W. Cancer chemotherapy: The case for therapeutic drug monitoring. Ther Drug Monit 2020;42(1):6–19.
[13] Dong B, Li S, Zhu S, Yi M, Luo S, Wu K. MiRNA-mediated EMT and CSCs in cancer chemoresistance. Exp Hematol Oncol 2021;10(1):12.
[14] Weersma RK, Zhernakova A, Fu J. Interaction between drugs and the gut microbiome. Gut 2020;69(8):1510–9.
[15] Zhao R, Coker OO, Wu J, Zhou Y, Zhao L, Nakatsu G, et al. Aspirin reduces colorectal tumor development in mice and gut microbes reduce its bioavailability and chemopreventive effects. Gastroenterology 2020;159(3):969–983.e964.
[16] Ting NL, Lau HC, Yu J. Cancer pharmacomicrobiomics: targeting microbiota to optimise cancer therapy outcomes. Gut 2022;71(7):1412–25.
[17] Zhu H, Swami U, Preet R, Zhang J. Harnessing DNA replication stress for novel cancer therapy. Genes (Basel) 2020;11(9).
[18] Haiser HJ, Turnbaugh PJ. Developing a metagenomic view of xenobiotic metabolism. Pharmacol Res 2013;69(1):21–31.
[19] Iida N, Dzutsev A, Stewart CA, Smith L, Bouladoux N, Weingarten RA, et al. Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. Science 2013;342(6161):967–70.
[20] Yuan L, Zhang S, Li H, Yang F, Mushtaq N, Ullah S, et al. The influence of gut microbiota dysbiosis to the efficacy of 5-Fluorouracil treatment on colorectal cancer. Biomed Pharmacother 2018;108:184–93.
[21] Yu T, Guo F, Yu Y, Sun T, Ma D, Han J, et al. Fusobacterium nucleatum promotes chemoresistance to colorectal cancer by modulating autophagy. Cell 2017;170(3):548–563.e516.
[22] Zhang S, Yang Y, Weng W, Guo B, Cai G, Ma Y, et al. Fusobacterium nucleatum promotes chemoresistance to 5-fluorouracil by upregulation of BIRC3 expression in colorectal cancer. J Exp Clin Cancer Res 2019;38(1):14.
[23] Chang CW, Lee HC, Li LH, Chiang Chiau JS, Wang TE, Chuang WH, et al. Fecal microbiota transplantation prevents intestinal injury, upregulation of toll-like receptors, and 5-fluorouracil/oxaliplatin-induced toxicity in colorectal cancer. Int J Mol Sci 2020;21(2).
[24] Pflug N, Kluth S, Vehreschild JJ, Bahlo J, Tacke D, Biehl L, et al. Efficacy of antineoplastic treatment is associated with the use of antibiotics that modulate intestinal microbiota. Oncoimmunology 2016;5(6):e1150399.

[25] Dyawanapelly S, Kumar A, Chourasia MK. Lessons learned from gemcitabine: Impact of therapeutic carrier systems and gemcitabine's drug conjugates on cancer therapy. Crit Rev Ther Drug Carrier Syst 2017;34(1):63–96.
[26] Gori S, Inno A, Belluomini L, Bocus P, Bisoffi Z, Russo A, et al. Gut microbiota and cancer: How gut microbiota modulates activity, efficacy and toxicity of antitumoral therapy. Crit Rev Oncol Hematol 2019;143:139–47.
[27] Geller LT, Barzily-Rokni M, Danino T, Jonas OH, Shental N, Nejman D, et al. Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine. Science 2017;357(6356):1156–60.
[28] Vande Voorde J, Sabuncuoğlu S, Noppen S, Hofer A, Ranjbarian F, Fieuws S, et al. Nucleoside-catabolizing enzymes in mycoplasma-infected tumor cell cultures compromise the cytostatic activity of the anticancer drug gemcitabine*. J Biol Chem 2014;289(19):13054–65.
[29] Csendes D, Gutlapalli SD, Prakash K, Swarnakari KM, Bai M, Manoharan MP, et al. Gastrointestinal microbiota and breast cancer chemotherapy interactions: A systematic review. Cureus 2022;14(11):e31648.
[30] Bawaneh A, Wilson AS, Levi N, Howard-McNatt MM, Chiba A, Soto-Pantoja DR, et al. Intestinal microbiota influence doxorubicin responsiveness in triple-negative breast cancer. Cancers (Basel) 2022;14(19).
[31] Kong C, Gao R, Yan X, Huang L, He J, Li H, et al. Alterations in intestinal microbiota of colorectal cancer patients receiving radical surgery combined with adjuvant CapeOx therapy. Sci China Life Sci 2019;62(9):1178–93.
[32] Sougiannis AT, VanderVeen BN, Enos RT, Velazquez KT, Bader JE, Carson M, et al. Impact of 5 fluorouracil chemotherapy on gut inflammation, functional parameters, and gut microbiota. Brain Behav Immun 2019;80:44–55.
[33] Shuwen H, Xi Y, Yuefen P, Jiamin X, Quan Q, Haihong L, et al. Effects of postoperative adjuvant chemotherapy and palliative chemotherapy on the gut microbiome in colorectal cancer. Microb Pathog 2020;149:104343.
[34] Terrisse S, Derosa L, Iebba V, Ghiringhelli F, Vaz-Luis I, Kroemer G, et al. Intestinal microbiota influences clinical outcome and side effects of early breast cancer treatment. Cell Death Differ 2021;28(9):2778–96.
[35] Lalla RV, Bowen J, Barasch A, Elting L, Epstein J, Keefe DM, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer 2014;120(10):1453–61.
[36] Carlotto A, Hogsett VL, Maiorini EM, Razulis JG, Sonis ST. The economic burden of toxicities associated with cancer treatment: review of the literature and analysis of nausea and vomiting, diarrhoea, oral mucositis and fatigue. Pharmacoeconomics 2013;31(9):753–66.
[37] Montassier E, Gastinne T, Vangay P, Al-Ghalith GA, Bruley des Varannes S, Massart S,, et al. Chemotherapy-driven dysbiosis in the intestinal microbiome. Aliment Pharmacol Ther 2015;42(5):515–28.
[38] Secombe KR, Coller JK, Gibson RJ, Wardill HR, Bowen JM. The bidirectional interaction of the gut microbiome and the innate immune system: Implications for chemotherapy-induced gastrointestinal toxicity. Int J Cancer 2019;144(10):2365–76.
[39] Osterlund P, Ruotsalainen T, Korpela R, Saxelin M, Ollus A, Valta P, et al. Lactobacillus supplementation for diarrhoea related to chemotherapy of colorectal cancer: a randomised study. Br J Cancer 2007;97(8):1028–34.
[40] Chang CW, Liu CY, Lee HC, Huang YH, Li LH, Chiau JC, et al. Lactobacillus casei variety rhamnosus probiotic preventively attenuates 5-fluorouracil/oxaliplatin-induced intestinal injury in a syngeneic colorectal cancer model. Front Microbiol 2018;9:983.
[41] Zhao L, Xing C, Sun W, Hou G, Yang G, Yuan L. Lactobacillus supplementation prevents cisplatin-induced cardiotoxicity possibly by inflammation inhibition. Cancer Chemother Pharmacol 2018;82(6):999–1008.
[42] Kee BK, Morris JS, Slack RS, Crocenzi T, Wong L, Esparaz B, et al. A phase II, randomized, double blind trial of calcium aluminosilicate clay versus placebo for the prevention of diarrhea in patients with metastatic colorectal cancer treated with irinotecan. Support Care Cancer 2015;23(3):661–70.
[43] Tang L, Li X, Wan L, Xiao Y, Zeng X, Ding H. Herbal Medicines for Irinotecan-Induced Diarrhea. Front Pharmacol 2019;10:182.
[44] Wang YH, Yao N, Wei KK, Jiang L, Hanif S, Wang ZX, et al. The efficacy and safety of probiotics for prevention of chemoradiotherapy-induced diarrhea in people with abdominal and pelvic cancer: a systematic review and meta-analysis. Eur J Clin Nutr 2016;70(11):1246–53.
[45] Zhu H, Lu C, Gao F, Qian Z, Yin Y, Kan S, et al. Selenium-enriched Bifidobacterium longum DD98 attenuates irinotecan-induced intestinal and hepatic toxicity in vitro and in vivo. Biomed Pharmacother 2021;143:112192.
[46] Jaggi AS, Singh N. Mechanisms in cancer-chemotherapeutic drugs-induced peripheral neuropathy. Toxicology 2012;291(1–3):1–9.
[47] Cuozzo M, Castelli V, Avagliano C, Cimini A, d'Angelo M, Cristiano C, et al. Effects of chronic oral probiotic treatment in paclitaxel-induced neuropathic pain. Biomedicines 2021;9(4).
[48] Juan Z, Chen J, Ding B, Yongping L, Liu K, Wang L, et al. Probiotic supplement attenuates chemotherapy-related cognitive impairment in patients with breast cancer: a randomised, double-blind, and placebo-controlled trial. Eur J Cancer 2022;161:10–22.
[49] Dalal N, Jalandra R, Bayal N, Yadav AK, Harshulika,. Sharma M et al.: Gut microbiota-derived metabolites in CRC progression and causation. J Cancer Res Clin Oncol 2021;147(11):3141–55.
[50] van der Beek CM, Dejong CHC, Troost FJ, Masclee AAM, Lenaerts K. Role of short-chain fatty acids in colonic inflammation, carcinogenesis, and mucosal protection and healing. Nutr Rev 2017;75(4):286–305.
[51] Rossi T, Vergara D, Fanini F, Maffia M, Bravaccini S, Pirini F. Microbiota-derived metabolites in tumor progression and metastasis. Int J Mol Sci 2020;21(16).
[52] Morrison DJ, Preston T. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. Gut Microbes 2016;7(3):189–200.
[53] Reichardt N, Duncan SH, Young P, Belenguer A, McWilliam Leitch C, Scott KP, et al. Phylogenetic distribution of three pathways for propionate production within the human gut microbiota. Isme j 2014;8(6):1323–35.
[54] Chen HM, Yu YN, Wang JL, Lin YW, Kong X, Yang CQ, et al. Decreased dietary fiber intake and structural alteration of gut microbiota in patients with advanced colorectal adenoma. Am J Clin Nutr 2013;97(5):1044–52.
[55] Ou J, Carbonero F, Zoetendal EG, DeLany JP, Wang M, Newton K, et al. Diet, microbiota, and microbial metabolites in colon cancer risk in rural africans and african americans. Am J Clin Nutr 2013;98(1):111–20.
[56] Sánchez-Alcoholado L, Laborda-Illanes A, Otero A, Ordóñez R, González-González A, Plaza-Andrades I, et al. Relationships of gut microbiota composition, short-chain fatty acids and polyamines with the pathological response to neoadjuvant radiochemotherapy in colorectal cancer patients. Int J Mol Sci 2021;22(17).
[57] Liberti MV, Locasale JW. The warburg effect: How does it benefit cancer cells? Trends Biochem Sci 2016;41(3):211–8.
[58] Geng HW, Yin FY, Zhang ZF, Gong X, Yang Y. Butyrate suppresses glucose metabolism of colorectal cancer cells via GPR109a-AKT signaling pathway and enhances chemotherapy. Front Mol Biosci 2021;8:634874.
[59] Singh N, Gurav A, Sivaprakasam S, Brady E, Padia R, Shi H, et al. Activation of Gpr109a, receptor for niacin and the commensal metabolite butyrate, suppresses colonic inflammation and carcinogenesis. Immunity 2014;40(1):128–39.
[60] Kim HJ, An J, Ha EM. Lactobacillus plantarum-derived metabolites sensitize the tumor-suppressive effects of butyrate by regulating the functional expression of SMCT1 in 5-FU-resistant colorectal cancer cells. J Microbiol 2022;60(1):100–17.
[61] Panebianco C, Villani A, Pisati F, Orsenigo F, Ulaszewska M, Latiano TP, et al. Butyrate, a postbiotic of intestinal bacteria, affects pancreatic cancer and gemcitabine response in in vitro and in vivo models. Biomed Pharmacother 2022;151:113163.
[62] Chen M, Jiang W, Xiao C, Yang W, Qin Q, Mao A, et al. Sodium butyrate combined with docetaxel for the treatment of lung adenocarcinoma A549 cells by targeting gli1. Onco Targets Ther 2020;13:8861–75.
[63] Guan X, Li W, Meng H. A double-edged sword: Role of butyrate in the oral cavity and the gut. Mol Oral Microbiol 2021;36(2):121–31.
[64] Donohoe DR, Collins LB, Wali A, Bigler R, Sun W, Bultman SJ. The Warburg effect dictates the mechanism of butyrate-mediated histone acetylation and cell proliferation. Mol Cell 2012;48(4):612–26.
[65] Freeman HJ. Effects of differing concentrations of sodium butyrate on 1,2-dimethylhydrazine-induced rat intestinal neoplasia. Gastroenterology 1986;91(3):596–602.
[66] Okumura S, Konishi Y, Narukawa M, Sugiura Y, Yoshimoto S, Arai Y, et al. Gut bacteria identified in colorectal cancer patients promote tumourigenesis via butyrate secretion. Nat Commun 2021;12(1):5674.
[67] Zidi O, Souai N, Raies H, Ben Ayed F, Mezlini A, Mezrioui S, et al. Fecal metabolic profiling of breast cancer patients during neoadjuvant chemotherapy reveals potential biomarkers. Molecules 2021;26(8).
[68] Miene C, Weise A, Glei M. Impact of polyphenol metabolites produced by colonic microbiota on expression of COX-2 and GSTT2 in human colon cells (LT97). Nutr Cancer 2011;63(4):653–62.
[69] Cardona F, Andrés-Lacueva C, Tulipani S, Tinahones FJ, Queipo-Ortuño MI. Benefits of polyphenols on gut microbiota and implications in human health. J Nutr Biochem 2013;24(8):1415–22.
[70] González-Sarrías A, Giménez-Bastida JA, Núñez-Sánchez M, Larrosa M, García-Conesa MT, Tomás-Barberán FA, et al. Phase-II metabolism limits the antiproliferative activity of urolithins in human colon cancer cells. Eur J Nutr 2014;53(3):853–64.
[71] Mirzaei S, Iranshahy M, Gholamhosseinian H, Matin MM, Rassouli FB. Urolithins increased anticancer effects of chemical drugs, ionizing radiation and hyperthermia on human esophageal carcinoma cells in vitro. Tissue Cell 2022;77:101846.
[72] Ghosh S, Singh R, Vanwinkle ZM, Guo H, Vemula PK, Goel A, et al. Microbial metabolite restricts 5-fluorouracil-resistant colonic tumor progression by sensitizing drug transporters via regulation of FOXO3-FOXM1 axis. Theranostics 2022;12(12):5574–95.
[73] González-Sarrías A, Miguel V, Merino G, Lucas R, Morales JC, Tomás-Barberán F, et al. The gut microbiota ellagic acid-derived metabolite urolithin A and its sulfate conjugate are substrates for the drug efflux transporter breast cancer resistance protein (ABCG2/BCRP). J Agric Food Chem 2013;61(18):4352–9.
[74] Ocvirk S, O'Keefe SJD. Dietary fat, bile acid metabolism and colorectal cancer. Semin Cancer Biol 2021;73:347–55.
[75] Pi Y, Wu Y, Zhang X, Lu D, Han D, Zhao J, et al. Gut microbiota-derived ursodeoxycholic acid alleviates low birth weight-induced colonic inflammation by enhancing M2 macrophage polarization. Microbiome 2023;11(1):19.
[76] Pearson T, Caporaso JG, Yellowhair M, Bokulich NA, Padi M, Roe DJ, et al. Effects of ursodeoxycholic acid on the gut microbiome and colorectal adenoma development. Cancer Med 2019;8(2):617–28.
[77] Wang H, Jatmiko YD, Bastian SE, Mashtoub S, Howarth GS. Effects of supernatants from escherichia coli nissle 1917 and faecalibacterium prausnitzii on intestinal epithelial cells and a rat model of 5-fluorouracil-induced mucositis. Nutr Cancer 2017;69(2):307–18.

[78] Pranzini E, Pardella E, Muccillo L, Leo A, Nesi I, Santi A, et al. SHMT2-mediated mitochondrial serine metabolism drives 5-FU resistance by fueling nucleotide biosynthesis. Cell Rep 2022;40(7):111233.
[79] Teng H, Wang Y, Sui X, Fan J, Li S, Lei X, et al. Gut microbiota-mediated nucleotide synthesis attenuates the response to neoadjuvant chemoradiotherapy in rectal cancer. Cancer Cell 2023;41(1):124–138.e126.
[80] Tintelnot J, Xu Y, Lesker TR, Schönlein M, Konczalla L, Giannou AD, et al. Microbiota-derived 3-IAA influences chemotherapy efficacy in pancreatic cancer. Nature 2023;615(7950):168–74.
[81] Peng Y, Nie Y, Yu J, Wong CC. Microbial metabolites in colorectal cancer: Basic and clinical implications. Metabolites 2021;11(3).
[82] Janney A, Powrie F, Mann EH. Host–microbiota maladaptation in colorectal cancer. Nature 2020;585(7826):509–17.
[83] Gaines S, van Praagh JB, Williamson AJ, Jacobson RA, Hyoju S, Zaborin A, et al. Western diet promotes intestinal colonization by collagenolytic microbes and promotes tumor formation after colorectal surgery. Gastroenterology 2020;158(4):958–970.e952.
[84] Yang J, Yu J. The association of diet, gut microbiota and colorectal cancer: what we eat may imply what we get. Protein Cell 2018;9(5):474–87.
[85] Icard P, Shulman S, Farhat D, Steyaert J-M, Alifano M, Lincet H. How the Warburg effect supports aggressiveness and drug resistance of cancer cells? Drug Resist Updat 2018;38:1–11.
[86] Brandhorst S. Fasting and fasting-mimicking diets for chemotherapy augmentation. Geroscience 2021;43(3):1201–16.
[87] Nencioni A, Caffa I, Cortellino S, Longo VD. Fasting and cancer: molecular mechanisms and clinical application. Nat Rev Cancer 2018;18(11):707–19.
[88] Forslund SK. Fasting intervention and its clinical effects on the human host and microbiome. J Intern Med 2023;293(2):166–83.
[89] Gatenby RA, Gillies RJ. Why do cancers have high aerobic glycolysis? Nat Rev Cancer 2004;4(11):891–9.
[90] Zorn S, Ehret J, Schäuble R, Rautenberg B, Ihorst G, Bertz H, et al. Impact of modified short-term fasting and its combination with a fasting supportive diet during chemotherapy on the incidence and severity of chemotherapy-induced toxicities in cancer patients - a controlled cross-over pilot study. BMC Cancer 2020;20(1):578.
[91] Kong C, Yan X, Liu Y, Huang L, Zhu Y, He J, et al. Ketogenic diet alleviates colitis by reduction of colonic group 3 innate lymphoid cells through altering gut microbiome. Signal Transduct Target Ther 2021;6(1):154.
[92] Ma DC, Anderson CM, Rodman SN, Buranasudja V, McCormick ML, Davis A, et al. Ketogenic diet with concurrent chemoradiation in head and neck squamous cell carcinoma: Preclinical and phase 1 trial results. Radiat Res 2021;196(2):213–24.
[93] Zahra A, Fath MA, Opat E, Mapuskar KA, Bhatia SK, Ma DC, et al. Consuming a ketogenic diet while receiving radiation and chemotherapy for locally advanced lung cancer and pancreatic cancer: The university of iowa experience of two phase 1 clinical trials. Radiat Res 2017;187(6):743–54.
[94] Tosti V, Bertozzi B, Fontana L. Health benefits of the mediterranean diet: Metabolic and molecular mechanisms. J Gerontol A Biol Sci Med Sci 2018;73(3):318–26.
[95] Lin XB, Farhangfar A, Valcheva R, Sawyer MB, Dieleman L, Schieber A, et al. The role of intestinal microbiota in development of irinotecan toxicity and in toxicity reduction through dietary fibres in rats. PLoS One 2014;9(1):e83644.
[96] Merra G, Noce A, Marrone G, Cintoni M, Tarsitano MG, Capacci A, et al. Influence of mediterranean diet on human gut microbiota. Nutrients 2020;13(1).
[97] Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol 2014;11(8):506–14.
[98] Doublier S, Cirrincione S, Scardaci R, Botta C, Lamberti C, Giuseppe FD, et al. Putative probiotics decrease cell viability and enhance chemotherapy effectiveness in human cancer cells: role of butyrate and secreted proteins. Microbiol Res 2022;260:127012.
[99] Jakubauskas M, Jakubauskiene L, Leber B, Horvath A, Strupas K, Stiegler P, et al. Probiotic supplementation suppresses tumor growth in an experimental colorectal cancer liver metastasis model. Int J Mol Sci 2022;23(14).
[100] Lee KA, Shaw HM, Bataille V, Nathan P, Spector TD. Role of the gut microbiome for cancer patients receiving immunotherapy: Dietary and treatment implications. Eur J Cancer 2020;138:149–55.
[101] Yao M, Xie J, Du H, McClements DJ, Xiao H, Li L. Progress in microencapsulation of probiotics: A review. Compr Rev Food Sci Food Saf 2020;19(2):857–74.
[102] Gibson GR, Hutkins R, Sanders ME, Prescott SL, Reimer RA, Salminen SJ, et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat Rev Gastroenterol Hepatol 2017;14(8):491–502.
[103] Taper HS, Roberfroid MB. Nontoxic potentiation of cancer chemotherapy by dietary oligofructose or inulin. Nutr Cancer 2000;38(1):1–5.
[104] Taper HS, Roberfroid MB. Possible adjuvant cancer therapy by two prebiotics–inulin or oligofructose. In Vivo 2005;19(1):201–4.
[105] Wang M, Yu F, Zhang Y, Chang W, Zhou M. The effects and mechanisms of flavonoids on cancer prevention and therapy: Focus on gut microbiota. Int J Biol Sci 2022;18(4):1451–75.
[106] Eid N, Enani S, Walton G, Corona G, Costabile A, Gibson G, et al. The impact of date palm fruits and their component polyphenols, on gut microbial ecology, bacterial metabolites and colon cancer cell proliferation. J Nutr Sci 2014;3:e46.
[107] Gu J, Sun R, Wang Q, Liu F, Tang D, Chang X. Standardized astragalus mongholicus bunge-curcuma aromatica salisb. extract efficiently suppresses colon cancer progression through gut microbiota modification in CT26-bearing mice. Front Pharmacol 2021;12:714322.
[108] Zhu XH, Lang HD, Wang XL, Hui SC, Zhou M, Kang C, et al. Synergy between dihydromyricetin intervention and irinotecan chemotherapy delays the progression of colon cancer in mouse models. Food Funct 2019;10(4):2040–9.
[109] Duan C, Tang X, Wang W, Qian W, Fu X, Deng X, et al. L-fucose ameliorates the carcinogenic properties of Fusobacterium nucleatum in colorectal cancer. Oncol Lett 2021;21(2):143.
[110] Yin L, Huang G, Khan I, Su L, Xia W, Law BYK, et al. Poria cocos polysaccharides exert prebiotic function to attenuate the adverse effects and improve the therapeutic outcome of 5-FU in Apc(Min/+) mice. Chin Med 2022;17(1):116.
[111] Huang J, Liu D, Wang Y, Liu L, Li J, Yuan J, et al. Ginseng polysaccharides alter the gut microbiota and kynurenine/tryptophan ratio, potentiating the antitumour effect of antiprogrammed cell death 1/programmed cell death ligand 1 (anti-PD-1/PD-L1) immunotherapy. Gut 2022;71(4):734–45.
[112] Schoener CA, Carillo-Conde B, Hutson HN, Peppas NA. An inulin and doxorubicin conjugate for improving cancer therapy. J Drug Deliv Sci Technol 2013;23(2):111–8.
[113] Motoori M, Yano M, Miyata H, Sugimura K, Saito T, Omori T, et al. Randomized study of the effect of synbiotics during neoadjuvant chemotherapy on adverse events in esophageal cancer patients. Clin Nutr 2017;36(1):93–9.
[114] Fukaya M, Yokoyama Y, Usui H, Fujieda H, Sakatoku Y, Takahashi T, et al. Impact of synbiotics treatment on bacteremia induced during neoadjuvant chemotherapy for esophageal cancer: A randomised controlled trial. Clin Nutr 2021;40(12):5781–91.
[115] Iida N, Mizukoshi E, Yamashita T, Terashima T, Arai K, Seishima J, et al. Overuse of antianaerobic drug is associated with poor postchemotherapy prognosis of patients with hepatocellular carcinoma. Int J Cancer 2019;145(10):2701–11.
[116] Verschueren MV, van der Welle CMC, Tonn M, Schramel F, Peters BJM, van de Garde EMW. The association between gut microbiome affecting concomitant medication and the effectiveness of immunotherapy in patients with stage IV NSCLC. Sci Rep 2021;11(1):23331.
[117] Nenclares P, Bhide SA, Sandoval-Insausti H, Pialat P, Gunn L, Melcher A, et al. Impact of antibiotic use during curative treatment of locally advanced head and neck cancers with chemotherapy and radiotherapy. Eur J Cancer 2020;131:9–15.
[118] Mohindroo C, Hasanov M, Rogers JE, Dong W, Prakash LR, Baydogan S, et al. Antibiotic use influences outcomes in advanced pancreatic adenocarcinoma patients. Cancer Med 2021;10(15):5041–50.
[119] Ahmed J, Kumar A, Parikh K, Anwar A, Knoll BM, Puccio C, et al. Use of broad-spectrum antibiotics impacts outcome in patients treated with immune checkpoint inhibitors. Oncoimmunology 2018;7(11):e1507670.
[120] Zhang W, Zhang J, Liu T, Xing J, Zhang H, Wang D, et al. Bidirectional effects of intestinal microbiota and antibiotics: a new strategy for colorectal cancer treatment and prevention. J Cancer Res Clin Oncol 2022;148(9):2387–404.
[121] Christophy R, Osman M, Mallat H, Achkar M, Ziedeh A, Moukaddem W, et al. Prevalence, antibiotic susceptibility and characterization of antibiotic resistant genes among carbapenem-resistant Gram-negative bacilli and yeast in intestinal flora of cancer patients in North Lebanon. J Infect Public Health 2017;10(6):716–20.
[122] Meunier A, Nerich V, Fagnoni-Legat C, Richard M, Mazel D, Adotevi O, et al. Enhanced emergence of antibiotic-resistant pathogenic bacteria after in vitro induction with cancer chemotherapy drugs. J Antimicrob Chemother 2019;74(6):1572–7.
[123] Biazzo M, Deidda G. Fecal microbiota transplantation as new therapeutic avenue for human diseases. J Clin Med 2022;11(14).
[124] Rossen NG, MacDonald JK, de Vries EM, D'Haens GR, de Vos WM, Zoetendal EG, et al. Fecal microbiota transplantation as novel therapy in gastroenterology: A systematic review. World J Gastroenterol 2015;21(17):5359–71.
[125] Huang C, Yi P, Zhu M, Zhou W, Zhang B, Yi X, et al. Safety and efficacy of fecal microbiota transplantation for treatment of systemic lupus erythematosus: An EXPLORER trial. J Autoimmun 2022;130:102844.
[126] Wardill HR, van der Aa SAR, da Silva Ferreira AR, Havinga R, Tissing WJE, Harmsen HJM. Antibiotic-induced disruption of the microbiome exacerbates chemotherapy-induced diarrhoea and can be mitigated with autologous faecal microbiota transplantation. Eur J Cancer 2021;153:27–39.
[127] Santana AB, Souto BS, Santos NCM, Pereira JA, Tagliati CA, Novaes RD, et al. Murine response to the opportunistic bacterium Pseudomonas aeruginosa infection in gut dysbiosis caused by 5-fluorouracil chemotherapy-induced mucositis. Life Sci 2022;307:120890.
[128] Smith MB, Kelly C, Alm EJ. Policy: How to regulate faecal transplants. Nature 2014;506(7488):290–1.

[129] He L, Yang H, Tang J, Liu Z, Chen Y, Lu B. Intestinal probiotics E. coli Nissle 1917 as a targeted vehicle for delivery of p53 and Tum-5 to solid tumors for cancer therapy. J Biol Eng 1917;2019(13):58.
[130] Ma Y, Liu Q, Hu A, Jiang S, Wang S, Liu R, et al. Construction and in vitro evaluation of a tumor acidic ph-targeting drug delivery system based on escherichia coli nissle 1917 bacterial ghosts. Bioengineering (Basel) 2022;9 (9).
[131] Xie S, Zhao L, Song X, Tang M, Mo C, Li X. Doxorubicin-conjugated Escherichia coli Nissle 1917 swimmers to achieve tumor targeting and responsive drug release. J Control Release 2017;268:390–9.
[132] Singh S, Kotla NG, Tomar S, Maddiboyina B, Webster TJ, Sharma D, et al. A nanomedicine-promising approach to provide an appropriate colon-targeted drug delivery system for 5-fluorouracil. Int J Nanomedicine 2015;10:7175–82.
[133] Han ZY, Chen QW, Fu ZJ, Cheng SX, Zhang XZ. Probiotic spore-based oral drug delivery system for enhancing pancreatic cancer chemotherapy by gut-pancreas-axis-guided delivery. Nano Lett 2022;22(21):8608–17.
[134] Luo Y, De Souza C, Ramachandran M, Wang S, Yi H, Ma Z, et al. Precise oral delivery systems for probiotics: A review. J Control Release 2022;352:371–84.
[135] Manrique P, Bolduc B, Walk ST, van der Oost J, de Vos WM, Young MJ. Healthy human gut phageome. Proc Natl Acad Sci U S A 2016;113(37):10400–5.
[136] Luong T, Salabarria AC, Roach DR. Phage Therapy in the resistance era: Where do we stand and where are we going? Clin Ther 2020;42(9):1659–80.
[137] Zheng DW, Dong X, Pan P, Chen KW, Fan JX, Cheng SX, et al. Phage-guided modulation of the gut microbiota of mouse models of colorectal cancer augments their responses to chemotherapy. Nat Biomed Eng 2019;3 (9):717–28.
[138] Hansen MF, Svenningsen SL, Røder HL, Middelboe M, Burmølle M. Big impact of the tiny: Bacteriophage-bacteria interactions in biofilms. Trends Microbiol 2019;27(9):739–52.
[139] Meng Q, Gao Q, Mehrazarin S, Tangwanichgapong K, Wang Y, Huang Y, et al. Fusobacterium nucleatum secretes amyloid-like FadA to enhance pathogenicity. EMBO Rep 2021;22(7):e52891.
[140] Macfarlane S, Macfarlane GT. Composition and metabolic activities of bacterial biofilms colonizing food residues in the human gut. Appl Environ Microbiol 2006;72(9):6204–11.
[141] Kabwe M, Brown TL, Dashper S, Speirs L, Ku H, Petrovski S, et al. Genomic, morphological and functional characterisation of novel bacteriophage FNU1 capable of disrupting Fusobacterium nucleatum biofilms. Sci Rep 2019;9 (1):9107.
[142] Zhang Y, Shen J, Shi X, Du Y, Niu Y, Jin G, et al. Gut microbiome analysis as a predictive marker for the gastric cancer patients. Appl Microbiol Biotechnol 2021;105(2):803–14.
[143] Zhang T, Zhang S, Jin C, Lin Z, Deng T, Xie X, et al. A predictive model based on the gut microbiota improves the diagnostic effect in patients with cholangiocarcinoma. Front Cell Infect Microbiol 2021;11:751795.
[144] Yu J, Feng Q, Wong SH, Zhang D, Qy L, Qin Y, et al. Metagenomic analysis of faecal microbiome as a tool towards targeted non-invasive biomarkers for colorectal cancer. Gut 2017;66(1):70–8.
[145] Feng Q, Liang S, Jia H, Stadlmayr A, Tang L, Lan Z, et al. Gut microbiome development along the colorectal adenoma-carcinoma sequence. Nat Commun 2015;6:6528.
[146] Gong TT, He XH, Gao S, Wu QJ. Application of machine learning in prediction of Chemotherapy resistant of Ovarian Cancer based on Gut Microbiota. J Cancer 2021;12(10):2877–85.
[147] Yi Y, Shen L, Shi W, Xia F, Zhang H, Wang Y, et al. Gut microbiome components predict response to neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer: A prospective. **Longitudinal Study** *Clin Cancer Res* 2021;27(5):1329–40.
[148] Li Y, Dong B, Wu W, Wang J, Jin H, Chen K, et al. Metagenomic analyses reveal distinct gut microbiota signature for predicting the neoadjuvant chemotherapy responsiveness in breast cancer patients. Front Oncol 2022;12:865121.
[149] Yamamura K, Izumi D, Kandimalla R, Sonohara F, Baba Y, Yoshida N, et al. Intratumoral fusobacterium nucleatum levels predict therapeutic response to neoadjuvant chemotherapy in esophageal squamous cell carcinoma. Clin Cancer Res 2019;25(20):6170–9.
[150] Wang A, Ling Z, Yang Z, Kiela PR, Wang T, Wang C, et al. Gut microbial dysbiosis may predict diarrhea and fatigue in patients undergoing pelvic cancer radiotherapy: a pilot study. PLoS One 2015;10(5):e0126312.
[151] Liu T, Xiong Q, Li L, Hu Y. Intestinal microbiota predicts lung cancer patients at risk of immune-related diarrhea. Immunotherapy 2019;11(5):385–96.
[152] Chamseddine AN, Ducreux M, Armand JP, Paoletti X, Satar T, Paci A, et al. Intestinal bacterial β-glucuronidase as a possible predictive biomarker of irinotecan-induced diarrhea severity. Pharmacol Ther 2019;199:1–15.
[153] Cheng KW, Tseng CH, Yang CN, Tzeng CC, Cheng TC, Leu YL, et al. Specific inhibition of bacterial β-glucuronidase by pyrazolo[4,3-c]quinoline derivatives via a pH-dependent manner to suppress chemotherapy-induced intestinal toxicity. J Med Chem 2017;60(22):9222–38.
[154] Coker OO, Liu C, Wu WKK, Wong SH, Jia W, Sung JJY, et al. Altered gut metabolites and microbiota interactions are implicated in colorectal carcinogenesis and can be non-invasive diagnostic biomarkers. Microbiome 2022;10(1):35.
[155] Shkoporov AN, Hill C. Bacteriophages of the human gut: The "known unknown" of the microbiome. Cell Host Microbe 2019;25(2):195–209.
[156] Zhao L, Shi Y, Lau HC, Liu W, Luo G, Wang G, et al. Uncovering 1058 novel human enteric dna viruses through deep long-read third-generation sequencing and their clinical impact. Gastroenterology 2022;163 (3):699–711.
[157] Lin Y, Lau HC, Liu Y, Kang X, Wang Y, Ting NL, et al. Altered mycobiota signatures and enriched pathogenic aspergillus rambellii are associated with colorectal cancer based on multicohort fecal metagenomic analyses. Gastroenterology 2022;163(4):908–21.
[158] Martinez-Guryn K, Leone V, Chang EB. Regional diversity of the gastrointestinal microbiome. Cell Host Microbe 2019;26(3):314–24.
[159] Kneis B, Wirtz S, Weber K, Denz A, Gittler M, Geppert C, et al. Colon cancer microbiome landscaping: Differences in right- and left-sided colon cancer and a tumor microbiome-ileal microbiome association. Int J Mol Sci 2023;24 (4).
[160] Liu W, Zhang X, Xu H, Li S, Lau HC, Chen Q, et al. Microbial community heterogeneity within colorectal neoplasia and its correlation with colorectal carcinogenesis. Gastroenterology 2021;160(7):2395–408.
[161] Wong CC, Yu J. Gut microbiota in colorectal cancer development and therapy. Nat RevClin Oncol 2023.
[162] Arozarena I, Wellbrock C. Phenotype plasticity as enabler of melanoma progression and therapy resistance. Nat Rev Cancer 2019;19(7):377–91.
[163] Hou Y, Dong L, Lu X, Shi H, Xu B, Zhong W, et al. Distinctions between fecal and intestinal mucosal microbiota in subgroups of irritable bowel syndrome. Dig Dis Sci 2022;67(12):5580–92.
[164] Nowicki C, Ray L, Engen P, Madrigrano A, Witt T, Lad T, et al. Comparison of gut microbiome composition in colonic biopsies, endoscopically-collected and at-home-collected stool samples. Front Microbiol 2023;14:1148097.



Shiyu Li: A Ph.D. candidate of Chinese University of Hong Kong, who has 10 publications on cancer field. The Ph.D. project is about the role of gut microbiota in cancer chemotherapy.

Shuangli Zhu: A Ph.D. candidate of Huazhong University of Science and Technology, who has 12 publications on cancer field.

Professor Jun Yu: Choh-Ming Li Professor of Medicine and Therapeutics Assistant Dean, Faculty of Medicine Director, The State Key Laboratory of Digestive Disease, The Chinese University of Hong Kong