

Role of the microbiome in systemic therapy for pancreatic ductal adenocarcinoma (Review)

XING HUANG*, MAO LI*, SHENGZHONG HOU and BOLE TIAN

Department of Pancreatic Surgery, West China Hospital of Sichuan University, Chengdu, Sichuan 610041, P.R. China

Received August 3, 2021; Accepted October 18, 2021

DOI: 10.3892/ijo.2021.5281

Abstract. A large body of evidence has revealed that the microbiome serves a role in all aspects of cancer, particularly cancer treatment. To date, studies investigating the relationship between the microbiome and systemic therapy for pancreatic ductal adenocarcinoma (PDAC) are lacking. PDAC is a high-mortality malignancy (5-year survival rate; <9% for all stages). Systemic therapy is one of the most important treatment choices for all patients; however, resistance or toxicity can affect its efficacy. Studies have supported the hypothesis that the microbiome is closely associated with the response to systemic therapy in PDAC, including the induction of drug resistance, or toxicity and therapy-related changes in microbiota composition. The present review comprehensively summarized the role of the microbiome in systemic therapy for PDAC and the associated molecular mechanisms in an attempt to provide a novel direction for the improvement of treatment response and proposed potential directions for in-depth research.

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1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a high-mortality malignancy with a 5-year survival rate of 9% for all stages and ~90% of patients are at advanced stages exhibiting a 5-year survival rate of 3% when diagnosed (1). PDAC is expected to become the second leading cause of cancer-related mortality worldwide within the next decade, due to its gradually increasing mortality rates (2). For patients who are not screened early enough, late-stage PDAC remains difficult to treat. Systemic chemotherapy, which includes neoadjuvant therapy, adjuvant therapy and first-line or subsequent therapy, is imperative for metastatic and locally advanced PDAC, as well as for other stages of PDAC. Gemcitabine has been established as the main first-line drug for PDAC chemotherapy. Other drugs, including albumin-bound paclitaxel, 5-fluorouracil (5-FU), capecitabine, cisplatin, irinotecan, oxaliplatin and erlotinib, are used in various combinations or as monotherapy, according to disease stage and patient status (3). However, due to acquired resistance or side effects during treatment, the efficacy for patients with PDAC is not satisfactory and the 5-year survival rate has not been significantly improved.

In recent years, an association between microbiomes and the occurrence and development of PDAC have been identified. Systems biology provides a more comprehensive and multiparametric understanding of drug metabolism. The microbiome, which is the comprehensive genomic information encoded by the microbiota and its ecosystem, products and host environment, has therefore been explored as a direction for therapy (4). Although the terms 'microbiota' and 'microbiome' are used interchangeably, the microbiota should be studied more comprehensively from the perspective of omics, while the functional microbiome is indispensable (5,6). Therefore, the 'microbiome' has been fully summarized and its function has been described. The composition of the microbiota is primarily determined by host genes and affected by extrinsic factors, including diet (7), antibiotics (8), surgery (9) and some drugs [e.g., proton pump inhibitors (10)]. In addition, pancreatic acini secrete peptides that can modulate the gut microbiota, relying on the Ca^{2+} channel calcium release-activated calcium channel protein 1 (11,12). The specific relationship between the microbiome and cancer, including gastrointestinal (13), breast (14), liver (15), esophageal cancer (16) and PDAC (17), has attracted the attention of researchers. Specifically, a large number of clinical studies have shown that the microbiome mediates the

Correspondence to: Professor Bole Tian, Department of Pancreatic Surgery, West China Hospital of Sichuan University, 37 Guoxue Alley, Chengdu, Sichuan 610041, P.R. China
E-mail: boletian0338@163.com

*Contributed equally

Key words: microbiome, pancreatic ductal adenocarcinoma, systemic therapy, resistance, toxicity

response to systemic therapy and that there are therapy-related changes in microbiota composition (18,19).

Initial evidence indicates that the microbiome is associated with PDAC (Table I). The microbiota can reach the pancreas via the circulatory system or the biliary/pancreatic duct, which potentially induces carcinogenesis. The human oral microbiome is a well-established independent risk factor associated with the development of PDAC (20-26), particularly *Porphyromonas gingivalis*, *Neisseria elongate*, *Streptococcus mitis* and *Fusobacterium* (17). Of note, *Fusobacterium* has been found to be a low-risk factor in the oral microbiota but is associated with increased cancer-specific mortality rates when present in PDAC tissue (20,27). Compared with benign pancreatic neoplasms and healthy cohorts, certain gut bacteria show a differential increase in abundance in patients with PDAC (28,29) and promote tumor growth in subcutaneous and liver metastasis models of PDAC by modulating immune response (30). In addition, the fecal microbiome differences between patients with PDAC and healthy subjects, or patients with pre-cancerous pancreatic lesions means that early, microbiome-based detection of PDAC is possible (31). The microbial diversity of intrapancreatic tumors in long-term survivors of PDAC is higher compared with that in short-term survivors (32); it also differed among PDAC cases with different stages of the disease (33). Mechanistically, a range of microbe-associated molecular patterns such as lipopolysaccharide (LPS), which are released by the microbiota and translocated into the pancreas, bind with selective Toll-like receptor (TLRs) and then activate signaling pathways, such as the NF- κ B and MAPK pathways, to exacerbate carcinogenesis through innate and adaptive immune suppression in PDAC (33,34), which may also synergize with K-ras (35). Furthermore, the mycobiome, particularly *Malassezia*, may also infiltrate PDAC tissues by driving the complement cascade through mannan-binding lectin activation (36). Antibiotics targeting unique microbiota constituents administered by orogastric gavage clearly inhibits PDAC progression and enhances adaptive immunity in a model of tumor protection (33). The receptor T2R38, which could be stimulated by a bacterial-derived signaling molecule, is expressed in tumor cells in patients with PDAC, as well as in tumor-derived cell lines and could link the microbiota to cancer (37). Gut microbiota metabolism may closely regulate PDAC progression through metabolite-sensing receptors (35,38). Admittedly, the underlying mechanism and link are complex, but functional research of the microbiome should improve our understanding of PDAC.

The majority of studies examining the microbiome in PDAC have focused on carcinogenicity, as the data on therapeutic action are preliminary. However, although the complex and important role of the microbiome in PDAC therapy requires in-depth study, related research is limited and the mechanisms involved remain to be fully elucidated. The aim of the present review was to outline recent microbiome research-related developments and interesting discoveries in systemic therapy drugs for PDAC and illustrate the underlying mechanisms. Promising research directions with regards to the involvement of the microbiome in PDAC treatment were also discussed and proposed.

2. The microbiome and PDAC systemic therapy resistance or toxicity

The majority of patients with PDAC require systemic therapy, whether that consists of surgery followed by adjuvant therapy, neoadjuvant therapy or palliative adjuvant therapy. However, since the majority of patients with PDAC develop resistance or toxicity to drugs, the treatment needs to be delivered at a lower dose or suspended before the scheduled end date, which leads to it being ineffective. Therefore, clarifying the complex mechanisms to improve treatment response is important. Functional research on the microbiota has suggested that it has the potential to induce PDAC treatment resistance or toxicity. In this section, the findings of previous studies with regards to the relationship between the microbiome and several drugs for the treatment of PDAC, including gemcitabine, 5-FU, capecitabine, oxaliplatin, irinotecan, cisplatin and erlotinib (Tables II and III), were described in detail (3).

Gemcitabine and paclitaxel. Gemcitabine has been widely used as a first-line drug for PDAC for decades (39). Several trials examining the efficacy of various drugs used either alone or in combination with gemcitabine achieved modest success, particularly nab-paclitaxel, a nanoparticle form of paclitaxel (40). Therefore, the majority of studies exploring the chemoresistance mechanisms in PDAC, including those focusing on the microbiome, focus on gemcitabine (41). Mycoplasma, which contains a number of nucleoside-metabolizing enzymes (42), could be a limiting factor for the anticancer efficiency of gemcitabine (dFdC-based chemotherapy) via cytidine deaminase (CDD), causing rapid drug catabolism in the tumor microenvironment (TME) (43). Furthermore, the deamination of gemcitabine has been shown to be indirectly potentiated by mycoplasma-derived pyrimidine nucleoside phosphorylase (PyNP) activity (43). Therefore, a CDD inhibitor can restore the activity of gemcitabine by co-administration, particularly with a thymidine phosphorylase (TP)/PyNP inhibitor (43). Geller *et al* (44) report that certain microbes, including *Gammaproteobacteria* and *Mycoplasma*, expressed the enzyme CDD, whose long form (CDDL) metabolizes gemcitabine into its inactive form (2',2'-difluorodeoxyuridine). *In vitro*, AsPC1 PDAC cells cultured with bacterial-conditioned medium are completely resistant to gemcitabine. Then, 113 human PDAC tissue samples were tested, 86 (76%) of which were positive for these bacteria, particularly *Gammaproteobacteria*. (44) Another study demonstrates that microbes present in the gut or intra-tumor regions influence the response to gemcitabine (45). These studies mainly indicate that the microbiome could directly degrade gemcitabine by metabolism, which is associated with the characteristics of the drug. Despite the lack of mouse models of PDAC, these results showed that bacterial species within PDAC tissues and the TME serve an important role in gemcitabine chemoresistance.

The combination of gemcitabine and albumin-bound paclitaxel has been upgraded as a category 1 recommendation (3). Kesh *et al* (46) found that microbial dysbiosis increases resistance to this combination. In a pancreatic tumor-bearing mouse model of type II diabetes, *Enterobacter cloacae* and carbohydrate- and lipid-metabolizing bacteria are

Table I. Summary of studies and changes in relative abundance on the related microbiota of pancreatic ductal adenocarcinoma.

Author, year	Sample	Methods	Specific microbiota	Animal or human	(Refs.)
Fan <i>et al</i> , 2018	Saliva	16S rRNA gene sequencing	High risk: <i>Porphyromonas gingivalis</i> , <i>Aggregatibacter</i> , <i>Actinomycetemcomitans</i> Low risk: <i>Fusobacteria</i>	Human	(20)
Torres <i>et al</i> , 2015		16S rRNA gene sequencing	↑ <i>Leptotrichia</i> , <i>Porphyromonas</i> ; ↓ <i>Neisseria</i> , <i>Aggregatibacter</i>	Human	(21)
Olson <i>et al</i> , 2017		16S rRNA gene sequencing	↑ <i>Firmicutes</i> (<i>Bacilli</i> , <i>Lactobacillales</i> , <i>Streptococcaceae</i> , <i>Streptococcus</i>) ↓ <i>Proteobacteria</i> (<i>Gammaproteobacteria</i> , <i>Pasteurellales</i> , <i>Pasteurellaceae</i> , <i>Haemophilus</i> , <i>Betaproteobacteria</i> , <i>Neisseriales</i> , <i>Neisseriaceae</i> , <i>Neisseria</i>)	Human	(22)
Farrell <i>et al</i> , 2012		16S rRNA gene sequencing	↑ <i>Firmicutes</i> , <i>Proteobacteria</i> , <i>Actinobacteria</i>	Human	(24)
Sun <i>et al</i> , 2020		16S rDNA high-throughput sequencing	↑ <i>Fusobacterium periodonticum</i> ; ↓ <i>Neisseria mucosa</i>	Human	(25)
Vogtmann <i>et al</i> , 2020		16S rRNA gene sequencing	↑ <i>Haemophilus</i>	Human	(26)
Half <i>et al</i> , 2015	Stool	16S rRNA gene sequencing	↑ <i>Sutterella</i> , <i>Veillonella</i> , <i>Bacteroides</i> , <i>Odoribacter</i> , <i>Akkermansia</i>	Human	(28)
Ren <i>et al</i> , 2017		16S rRNA gene sequencing	↑ <i>Prevotella</i> , <i>Veillonella</i> , <i>Klebsiella</i> , <i>Selenomonas</i> , <i>Hallella</i> , <i>Enterobacter</i> , <i>Cronobacter</i> ↓ <i>Gemmiger</i> , <i>Bifidobacterium</i> , <i>Coprococcus</i> , <i>Clostridium</i> IV, <i>Blautia</i> , <i>Flavonifractor</i> , <i>Anaerostipes</i> , <i>Butyrivibrio</i> , <i>Dorea</i>	Human	(29)
Sethi <i>et al</i> , 2018		16S rRNA gene sequencing and depleting microbiota	↓ <i>Bacteroidetes</i> , <i>Firmicutes</i>	Subcutaneous KPC bearing mice	(30)
Half <i>et al</i> , 2019		16S rRNA gene sequencing	↑ <i>Firmicutes</i> phylum	Human	(31)
Mendez <i>et al</i> , 2020		16S rRNA gene sequencing	↓ <i>Actinobacteria</i> , <i>Deferribacteres</i> , <i>Firmicutes</i> , <i>Proteobacteria</i>	KPC mice	(38)
Riquelme <i>et al</i> , 2019	Tumor tissue	16S rRNA gene sequencing	↑ <i>Pseudoxanthomonas</i> , <i>Streptomyces</i> , <i>Saccharopolyspora</i> , <i>Bacillus clausii</i>	Human: long-term vs. short-term	(32)
Pushalkar <i>et al</i> , 2018		16S rRNA gene sequencing	I/II stage: ↑ <i>Veillonella</i> , <i>Streptococcus</i> IV stage: ↓ <i>Phascolarctobacterium</i> , <i>Alcaligenaceae</i> , <i>Synergistaceae</i> , <i>Paraprevotellaceae</i>	Human	(33)
Mitsuhashi <i>et al</i> , 2015		TaqMan primer/probe sets	<i>Fusobacterium</i> species: associated with a worse prognosis of pancreatic cancer	Human	(27)
Geller LT <i>et al</i> , 2017		16S rDNA sequencing	↑ <i>Proteobacteria</i> , <i>Firmicutes</i> , <i>Actinobacteria</i>	Human	(44)
Aykut <i>et al</i> , 2019	Stool and tumor tissue	18S rRNA sequencing	↑ <i>Malassezia</i>	Animal & Human	(36)

↑/↓: means the relative abundance of microbiota is increase or decrease; KPC mice, Pdx1Cre; LSL-KrasG12D; Trp53R172H mice.

Table II. Impact and mechanism of microbiome on efficacy of drugs for pancreatic ductal adenocarcinoma.

Author, year	Drug	Main microbiota	Outcome	Mechanism	(Refs.)
Vande <i>et al</i> , 2014	Gemcitabine	<i>Mycoplasmas</i>	Resistance	These bacteria metabolize it into inactive by CDD	(43,44)
Geller <i>et al</i> , 2017		<i>Gammaproteobacteria</i>			
Kesh <i>et al</i> , 2020	Paclitaxel	<i>Enterobacter cloacae</i>	Resistance	The microbial metabolite act as anti-oxidants	(46)
Bronckaers <i>et al</i> , 2018	5-FU	<i>Mycoplasma hyorhinis</i>	Resistance	The bacteria degrade it into inactive by TP	(59)
Yu <i>et al</i> , 2017		<i>Fusobacterium nucleatum</i>	Resistance	By activating the autophagy pathway or upregulating the expression of BIRC3	(60,61)
Zhang <i>et al</i> , 2019					
Loman BR <i>et al</i> , 2019		<i>E. coli</i> and <i>Comamonas</i>	Increased efficacy	Bacterial ribonucleotide metabolism (48) and bacterial vitamin B6, B9	(63)
Scott TA <i>et al</i> , 2017					
Pflug <i>et al</i> , 2016	Cisplatin	<i>Gram-positive bacteria</i>	Negative impact on its effect	Gram-positive bacterial antibiotics could weaken its anti-tumor effect, but the specific mechanism is unknown	(67)
Iida <i>et al</i> , 2013	Oxaliplatin	No specific bacteria	Resistance	Treatment with ABX decrease ROS production	(76)
Geller <i>et al</i> , 2017		<i>Klebsiella pneumoniae</i> , <i>Pseudomonas aeruginosa</i> , <i>Citrobacter freundii</i>	Resistance	Unknown	(44)
Yu <i>et al</i> , 2017	Irinotecan	<i>Fusobacterium nucleatum</i>	Resistance	By activating the autophagy pathway	(60)
Heshiki <i>et al</i> , 2020	Erlotinib	<i>B. ovatus</i> and <i>B. xylanisolvens</i>	Increased efficacy	Synergistically upregulated the expression of chemokines involved in the recruitment of T cells	(95)

CDD, Cytidine deaminase; 5-FU, 5-fluorouracil; TP, Thymidine phosphorylase; ROS, reactive oxygen species; ABX, an antibiotic cocktail of antibiotics.

Table III. Effect and mechanism of microbiome on toxicity of drugs for pancreatic ductal adenocarcinoma.

Author, year	Drug	Main microbiota	Outcome	Mechanism	(Refs.)
Ramakrishna C <i>et al</i> , 2019	Gemcitabine Paclitaxel	- <i>Akkermansia muciniphila</i>	- CIPN	- Decreased the abundance of this bacteria and lead to exposure to bacterial metabolites and products, which altered brain function via gut-immune-brain	(49)
Stringer AM <i>et al</i> , 2019 Saegusa Y <i>et al</i> , 2018 Nakayama H <i>et al</i> , 1997	5-FU	↓ <i>Lactobacillus</i> , <i>Streptococcus</i> ↑ <i>Clostridium</i> , <i>Staphylococcus</i> <i>Bacteroides</i> spp	Intestinal mucositis Death	5-FU alter the microbiota diversity and lead to decrease of mucin secretion This specie could inactivate the detoxification enzyme by BVU, which lead to the accumulation of 5-FU in the blood	(52,55) (57)
Gui QF <i>et al</i> , 2015 Wu CH <i>et al</i> , 2019 Shen S <i>et al</i> , 2017	Cisplatin Oxaliplatin	Unknow the specific microbiota Unknow the specific microbiota	Gastrointestinal injury CIPN	Unknow, might be associated with gut microbiome dysbiosis Oxaliplatin may directly alter the gut microbiota and increase the DRG LPS levels, which target targets TLR4 expressed on hematopoietic cells and then stimulates the primary macrophages, leading to provoke inflammatory cytokine production	(69,70) (80)
Forsgård RA <i>et al</i> , 2017 Chang C-W <i>et al</i> , 2018 Sparreboom A <i>et al</i> , 1998 Takasuna K <i>et al</i> , 1996 Brandi G <i>et al</i> , 2006 Ribeiro RA <i>et al</i> , 2016	Irinotecan Erlotinib	Unknow the specific microbiota -	Gastrointestinal injury Delayed-onset diarrhea Intestinal mucositis and pain	Unknow, might be associated with gut microbiome dysbiosis The β-glucuronidase secreted by gut microbiota dissociate SN-38G to SN-38 TLR4-dependent mechanisms	(82,83) (87,88) (89,92)
CIPN, Chemotherapy induced peripheral neuropathy; 5-FU, 5-fluorouracil; BVU, (E)-5-(2-bromovinyl) uracil; DRG, Dorsal Root Ganglion; LPS, lipopolysaccharides; TLR4, Toll-like receptor.					

enriched. This enrichment of microbial metabolites prevents tumor cells from chemotherapy-induced accumulation of reactive oxygen species, leading to resistance (46); however, in that study, the treatment regimen was a combination of gemcitabine and paclitaxel and no study has yet focused on microbiome-induced paclitaxel monotherapy resistance. Although lactic acid bacteria, bifidobacteria and other bacteria of intestinal origin are not susceptible to paclitaxel (47), the bacterial populations are altered in paclitaxel-treated mice: butyrate-producing bacteria, including *Roseburia*, *Eubacterium* and *Erysipelotrichaceae*, are depleted (48) and paclitaxel treatment decreases the abundance of *Akkermansia muciniphila* and alters that of other bacterial taxa, which are drivers of chemotherapy-induced peripheral neuropathy (CIPN) (49). In addition, paclitaxel-containing chemotherapeutic combinations are more likely to result in *Clostridioides difficile* infection (50). Therefore, the anti-tumor effect of paclitaxel could be improved by reversing paclitaxel-induced gut microbiota dysbiosis (51).

Fluoropyrimidine. Fluoropyrimidine is also a first-line chemotherapeutic drug for patients with PDAC, including 5-FU, capecitabine and TAS-1. 5-FU is frequently administered alongside FOLFIRINOX/modified FOLFIRINOX and with or without leucovorin (3). Capecitabine, a precursor of 5-FU, can be administered alone or co-administered with gemcitabine to patients with PDAC (3). The majority of studies on 5-FU focus on its effects on the abundance of microbiota constituents and induction of mucositis (52-54). The main mechanisms of toxicity have been demonstrated. First, 5-FU alters microbiota diversity by decreasing *Lactobacillus* and *Streptococcus* abundance and increasing *Clostridium* and *Staphylococcus* abundance, leading to a decrease in the secretion of mucin, a principal factor in the physiological defense of the gastrointestinal mucosa (52,55). Therefore, supplementation with the genera *Lactobacillus* and *Bifidobacterium* could protect the human gastrointestinal tract from chemotherapy (56). Secondly, the lack of a detoxification enzyme of 5-FU (hepatic dihydropyrimidine dehydrogenase) may lead to an increase in the systemic concentrations of 5-FU in the blood and enhanced toxicity. The gut microbiota serves a critical role in that process. Specific bacteria, including *Bacteroides* species (*B. vulgatus*, *B. thetaiotaomicron*, *B. fragilis*, *B. uniformis* and *B. eggerthii*) can hydrolyze sorivudine to (E)-5-(2-bromovinyl) uracil, which inactivates the detoxification enzyme (57).

At present, the understanding of whether the gut microbiota influences the antitumor efficacy of 5-FU treatment is limited. A previous study proposes that 5-FU together with ABX, an antibiotic cocktail, markedly reduces the antitumor effect of 5-FU and the gut bacterial diversity and communities show significant changes compared with those after 5-FU alone or 5-FU plus probiotic treatments (58). This means that the gut flora dysbiosis contributes to the induction of 5-FU resistance. *Mycoplasma hyorhinis*, which was mentioned in the gemcitabine and paclitaxel section, also degrades fluoropyrimidines, including 5-FU, by TP to their inactive bases. By contrast, capecitabine, which must be metabolized to 5-fluoro-5'-deoxyuridine (5'DFUR), can benefit from TP activity (59). *Fusobacterium nucleatum*, an anaerobic bacterium that is parasitic in the oral cavity and highly abundant

in the gut microbiota, may promote 5-FU and oxaliplatin resistance by targeting TLR4 and myeloid differentiation primary response 88 (MYD88) innate immune signaling and then downregulating the expression of microRNA (miR)-18a* and miR-4802, which activate the autophagy pathway by increasing Unc-51 like autophagy activating kinase 1 and autophagy related 7 expression (60). In addition, another study demonstrated that *F. nucleatum* confers resistance to 5-FU by upregulating the expression of baculoviral IAP repeat containing 3 via the TLR4/NF- κ B pathway (61). These two studies suggest that fully elucidating the mechanism of the specific microbiota constituents inducing chemoresistance poses a major challenge as the same bacteria may have two or several regulatory pathways that alter drug response. García-González *et al* (62) found that *Escherichia coli* and *Comamonas* increase 5-FU efficacy by bacterial nucleotide metabolism and lead to the sterility of *C. elegans*, a powerful model system to study the effects of the microbiota on chemotherapeutics. In addition to this mechanism, another study reports that *E. coli* vitamin B6 and B9 metabolism are essential for 5-FU efficacy in the same *C. elegans* model (63).

Platinum salt. Cisplatin is a platinum-based potent antitumor agent used for PDAC, along with gemcitabine, but only for patients with known breast cancer type 1/2 or partner and localizer of BRCA2 mutations (3,64). Cisplatin causes tumor cytotoxicity by forming platinum DNA adducts and intra-strand cross-links, as well as through the modulation of the immune system (65,66). Few studies have focused on microbiome-mediated cisplatin resistance (67,68). Gram-positive bacterial antibiotics can weaken its antitumor effect (67), but the specific mechanism remains to be elucidated. In addition, the majority of gastrointestinal toxicities caused by cisplatin have been attributed to various events, such as oxidative stress and inflammation (68). Although there is no direct evidence that the microbiome induces toxicity, the combination of cisplatin with the commensal microbiota or agents that balance it could ameliorate cisplatin-induced gastrointestinal toxicity (69-72), as well as other adverse effects (73-75). These studies suggest the existence of a crucial intrinsic link between the microbiome and cisplatin, but additional research should focus on and clarify the mechanism.

Oxaliplatin, a third-generation platinum-based chemotherapeutic drug, has been approved for the first-line treatment of PDAC in FOLFIRINOX/modified FOLFIRINOX strategies (3). Iida *et al* (76) suggest that an intact commensal microbiota is indispensable for optimal responses to cancer therapy with oxaliplatin and that ABX impairs the effect of oxaliplatin by decreasing reactive oxygen species (ROS) production, which serves a crucial role in DNA damage and apoptosis (77). Although the complex microbiome holds infinite possibilities to control the response of oxaliplatin (76), the exact bacteria that serve a pivotal role are unknown. By contrast, Geller *et al* (44) found that certain bacteria can mediate resistance to oxaliplatin, including *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Citrobacter freundii*, but not CDDL-mediated resistance and the mechanism was unclear. In another study, Yu *et al* (60) demonstrate that *F. nucleatum* induces oxaliplatin resistance by targeting TLR4 and MYD88 innate immune signaling and specific miRs to

activate the autophagy pathway, similar to 5-FU. Although the microbiome can either disturb or promote the effect of oxaliplatin, it is unclear which microbes are involved or the specific mechanisms underlying their involvement.

The efficacy of oxaliplatin is limited by peripheral neuropathies, as well as gastrointestinal toxicity (78,79), but whether the microbiota induces or mediates oxaliplatin toxicity has rarely been reported. Shen *et al* (80) reports that the gut microbiota may promote the development of oxaliplatin-induced pain, which can be reduced in germ-free mice and mice pretreated with antibiotics. Mechanistically, the dorsal root ganglion (DRG) is a key anatomical site for CIPN pathogenesis (81). Oxaliplatin may directly alter the gut microbiota and increase LPS levels in the DRG (80). LPS derived from the gut microbiota targets TLR4, which is expressed on hematopoietic cells and then stimulates primary macrophages, leading to the production of inflammatory cytokines in the DRG, such as IL-6 and TNF- α (80). Gastrointestinal injury is one of the toxicities induced by oxaliplatin, an effect that may be associated with alterations in the gut microbiota and activation of inflammatory processes (82,83). Accordingly, fecal microbiota transplantation (FMT) can alleviate the injury (84).

Irinotecan. Although FOLFIRINOX causes marked improvements in patients with metastatic PDAC compared with gemcitabine, the 3/4 toxicity rate is clearly greater (85), which always leads to a dose reduction. Irinotecan (also known as CPT-11) is the main drug in the FOLFIRINOX regimen that occasionally induces severe toxicities, which limit its use and efficacy (86). Delayed-onset diarrhea is a common clinical adverse effect. The most likely mechanism of the induction of severe diarrhea is that the β -glucuronidase secreted by the gut microbiota dissociates SN-38G to SN-38, which is responsible for both antitumor activity and dose-limiting toxicity (87,88). This underlying mechanism reveals that the gut microflora serves a critical role in the intestinal toxicity of irinotecan (89), even though the association appears to be controversial and mechanisms other than this enzyme, such as TLR4-dependent mechanisms (90), may be involved in irinotecan treatment (91,92).

Erlotinib. Erlotinib, an EGFR tyrosine kinase inhibitor, increases overall survival when combined with gemcitabine (93) and this combination therapy is another option for patients with locally advanced or metastatic disease; it has a good performance status and is a category 1 recommendation for patients with metastatic disease in the National Comprehensive Cancer Network guidelines (3). There is little research on the relationship between the microbiome and erlotinib. Two studies indicate that certain bacteria of intestinal origin had no susceptibility to erlotinib and did not induce changes in intestinal tissue morphology, but whether there were changes in the abundance of the gut microbiome remain unknown (47,94). Heshiki *et al* (95) found that baseline microbiota composition could predict treatment response and the responder bacteria (*Bacteroides ovatus* and *B. xylanisolvens*) increase the efficacy of erlotinib in mice more than the non-responder bacteria (*Cenarchaeum symbiosum* and *Ruminococcus gnavus*) when administered by oral gavage. Mechanistically, the responder

bacteria may synergistically upregulate chemokines involved in T-cell recruitment and then enhance erlotinib efficacy (95).

3. Further directions

Pharmacomicrobiomics, a new discipline exploring the interactions between drugs and microbes (96), has the potential to broaden our understanding of the interplay between the microbiome and systemic therapy for PDAC. In addition, clinical metagenomic next-generation sequencing has provided a glimpse into the monitoring of chemotherapy regimens (97). In addition, the increased knowledge obtained in this field can potentially generate novel chemotherapeutic or subsequent therapy approaches to enhance efficacy and abrogate side effects by manipulating the α - and β -diversity of the microbiota to individualize treatment. The present review provided a detailed overview of the association between the microbiome and systemic therapy drugs for PDAC. However, since the majority of the studies' objectives are not PDAC, the evidence obtained in the present study remains limited. Therefore, carrying out research to further elucidate the role of the microbiome in PDAC systemic therapy is urgent. From the perspective of the present study, four main aspects need additional attention in future research (Fig. 1).

Baseline gut microbiome for individualized chemotherapy programs for patients with PDAC. Numerous clinical studies have investigated whether the baseline gut microbiota predicts the clinical response to systemic cancer therapy or bacterial infection (19,98-100). Aarnoutse *et al* (101) profile the microbiota composition before, during and after three cycles of systemic treatment with capecitabine or TAS-102 and attempt to detect a microbiota composition that predicts chemotoxicity in patients with metastatic and/or resectable colorectal cancer.

Heshiki *et al* (95) investigate the role of the gut microbiota in a cancer patient cohort, which comprised 26 patients with eight different types of cancer (including PDAC) treated with targeted chemotherapy (n=15), or a combination of cytotoxic or targeted chemotherapy with immunotherapy (n=11). Although the cancer type varies, a dendrogram shows that the cluster tends to be closely based on therapeutic effects rather than on type of cancer or therapeutic regimens (95). Based on the treatment outcome, the patients are grouped into responders and non-responders and then the differences in intestinal microbial composition and functionality are identified. Next, a classification model is built that includes species and pathways that could predict the response to anticancer treatments. In an independent validation cohort, the prediction models achieved high accuracy (area under curve=0.75) (95).

In addition, the baseline gut microbiome can also be used to predict the toxicity of chemotherapy. Stringer *et al* (102) analyze stool and serum samples from 26 patients with cancer receiving chemotherapy. The type of cancer and chemotherapy regimen both differed from patient to patient; the latter included capecitabine, cisplatin/5-FU, FOLFOX, 5-FU/folinic acid, COFF plus paclitaxel and carboplatin plus gemcitabine. Specific bacteria were enriched (including *E. coli* and *Staphylococcus* spp.) or depleted (including *Lactobacillus* spp., *Bifidobacterium* spp., *Bacteroides* spp. and *Enterococcus* spp.) in the majority of patients with chemotherapy-induced

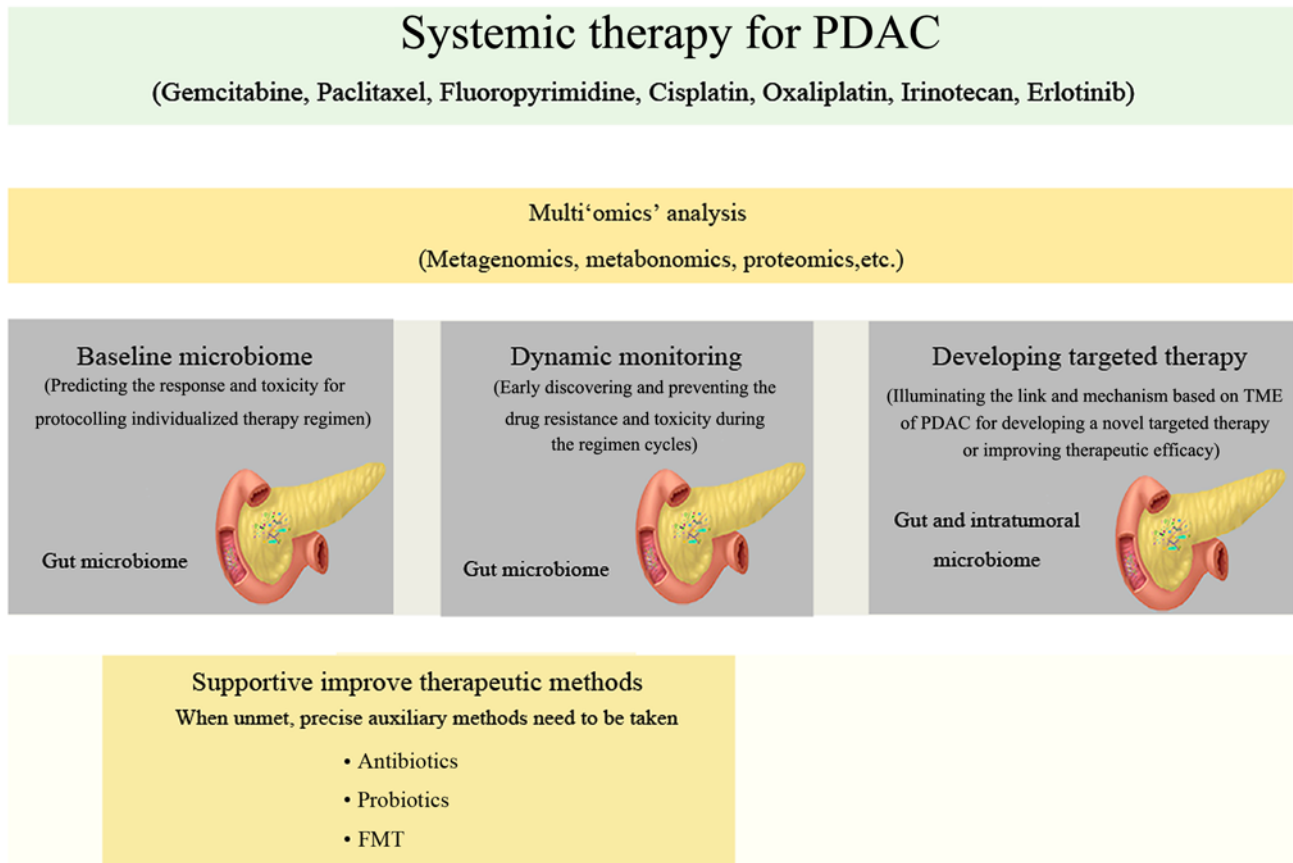


Figure 1. Further interrelated directions of microbiome research for improving systemic therapy for PDAC. Baseline gut microbiome sequencing and multi 'omics' functional analysis can be used to establish a prediction model for selecting a precision chemotherapy regimen. During the cycles of chemotherapy, dynamic monitoring of the changes in the gut microbiome can contribute to the early discovery of upcoming resistance or toxicity, so that certain precise interventions for balancing microbiome dysbiosis can be carried out. However, the microbiome is complex and further research should focus not only on the gut, but also on the tissue, in search of a novel targeted systemic therapy or methods for improving therapeutic efficacy. PDAC, pancreatic ductal adenocarcinoma; TME, tumor microenvironment; FMT, fecal microbiota transplantation.

diarrhea (CD) and alterations in inflammation and circulating matrix metalloproteinases were observed (102). These changes may serve as predictive biomarkers of chemotherapeutic toxicity. In addition, the biomarkers based on the baseline gut microbiome could be combined with additional biomarkers, including metabolites.

Relevant clinical studies of PDAC are not yet available. However, ongoing or previous studies have suggested that the baseline microbiota may be able to predict treatment response. Related clinical research on PDAC exploring different regimens, stages and performance statuses should therefore be performed. This research can be more comprehensive, investigating not only the gut or intratumor microbiota but also the related metabolites and other small molecules, which could be generalized to the aforementioned microbiome. That accumulated knowledge could help build a systemic and comprehensive prediction model for the response to chemotherapy regimens.

Dynamic monitoring of changes in the gut microbiome during the chemotherapy cycle and exploration of the function-mediated diversity mechanism. Systemic cancer therapies can affect the entire body, as well as the human microbiota composition and abundance, including that of gut and intratumor environment microbiota. The majority of

existing studies have focused on the link between intestinal barrier dysfunction and toxicity (44,48,52,103-108). In addition, whether the drugs induce changes in the microbiome and then lead to resistance is unclear. This phenomenon is called function-mediated diversity and certain studies have hinted at that possibility.

In animal studies, Lin *et al* (103) describe the microbiota changes during irinotecan therapy. Following irinotecan chemotherapy, cecal *Clostridium* cluster XI and *Enterobacteriaceae*, which do not mediate CD, are increased and antimicrobial activity is excluded *in vitro* by irinotecan and SN-38 (103). Panebianco *et al* (104) demonstrate the influence of gemcitabine chemotherapy on the fecal microbiota of PC-xenografted mice. At the phylum level, *Firmicutes* and *Bacteroidetes* are considerably depleted and *Proteobacteria* and *Verrucomicrobia* are enriched. For *Proteobacteria*, one study demonstrates its ability to induce resistance to gemcitabine (44). At the species level, *Akkermansia muciniphila* and *E. coli* are significantly enriched, while *B. acidifaciens* is depleted (104). For 5-FU, the majority of studies have described the influence of chemotherapy-induced mucositis, mainly due to microbial dysbiosis, as mentioned above. A detailed study shows that the changes in jejunum, colon and fecal samples are different (52). *Lactobacillus* spp. and *Streptococcus* spp. are all depleted in the jejunum and

colon, but *Clostridium* spp. are depleted and *Escherichia* spp. are enriched in the jejunum, while *Enterococcus* spp. are depleted in the colon. In the fecal samples, the results show a decreasing trend in *Lactobacillus* spp. and *Bacteroides* spp. and an increasing trend in *E. coli* (52). Paclitaxel-treated mice also exhibit a decrease in fecal bacterial diversity (48). Chemotherapy drugs induce changes in the microbiome not only in composition and abundance but also in the emergence of antibiotic-resistant pathogenic bacteria (105).

In a clinical study, Zwielehner *et al* (106) investigate the chemotherapy-induced changes in fecal microbiota. After analyzing the feces of 17 cancer patients before and after the chemotherapy cycle at four time points, the percentage of *Clostridium* cluster XIVa decreased from 22±13 to 19±12%, while the average proportions of *Bacteroides*, *Bifidobacteria* and *Clostridium* cluster IV increased (106). The changes among the four time points were also shown (106). Due to the variety of types of cancer and chemotherapy regimens, the conclusions of that study are limited and should be further confirmed in a more rigorous design. Another study identifies a significant decrease in the abundance of *Firmicutes* and *Actinobacteria* and increase in the abundance of *Proteobacteria*, as compared with those before chemotherapy in fecal samples (107), but the specific regimen is unknown. Kong *et al* (108) performed a study to identify alterations in the gut microbiota of colorectal cancer patients treated with adjuvant chemotherapy (capecitabine plus oxaliplatin) following radical surgery. Although no significant difference in the diversity and composition of the gut microbiota was observed among the various time points chemotherapy, the dynamic changes revealed by heat map clustering analysis showed that the abundance of *Bacteroidetes* was increased, while that of *Firmicutes* was decreased after chemotherapy compared to before chemotherapy (108).

These limited studies suggest that multiple cycles of chemotherapy cause changes in the gut microbiota and that altered organisms may cause drug resistance or sensitivity. This alteration in microbial diversity may be mediated and accelerated by the functional response to chemotherapy, with the microecosystems changing towards a more favorable environment (109), which has been destroyed by systemic chemotherapy. However, no related research has been conducted for PDAC. Concentrating on dynamic changes and functional response diversity will help clinicians deal with resistance or impede infection quickly and effectively.

Identifying the mechanism to develop a novel targeted therapy or improve therapeutic efficacy. The microbiota is complex and certain studies have illustrated that certain bacteria can mediate the resistance and toxicity of certain chemotherapy drugs. However, the specific mechanism may be multifactorial. For example, *Fusobacterium*, an oral bacterium detected in PDAC tissue (20,27), mediates 5-FU resistance by activating the autophagy and TLR4/NF- κ B pathways (60,61). In addition, identifying specific bacteria and mechanisms is conducive to developing a new targeted therapy to improve resistance. For irinotecan, targeted gut microbial enzyme inhibitors may be a new potential method to alleviate gastrointestinal tract toxicity and enhance efficacy (110,111). Due to the structural

and functional differences in β -glucuronidases from the human gut microbes (112,113), β -glucuronidase inhibitors should be selective and not affect the survival of the microbiota (114,115); therefore, the molecular mechanism should be specific. In addition, when analyzing the species and functional composition of the gut microbiome, the focus cannot only be placed on the abundant species, which do not always equate to abundant molecular functions (116). Functional analysis needs to be specific to a particular microbiome, including species with low abundance.

In addition, an increased understanding of the complex mechanisms underlying the role of the microbiome in the systemic therapy of PDAC needs to include the role of the microbiome in the TME, which is composed of a minority of malignant cells, endothelial cells, immune cells, fibroblasts and extracellular matrix (117), as well as the microbiota. Therapeutic failures of chemotherapy, particularly gemcitabine, have been attributed to the PDAC microenvironment (118). Given the complexity of the PDAC TME, the cause of resistance to chemotherapy is multifactorial and the microbiome may serve a moderate role. For example, intrapancreatic and gut-specific microbes serve as helpers in the shaping of the immunosuppressive PDAC TME, which leads to tumor-associated macrophages (TAMs) becoming highly abundant in PDAC, ranging from M1-like TAMs to immune-suppressive M2-like TAMs (33). In this process, deoxycytidine macrophages release competitively inhibits gemcitabine uptake and metabolism and leads to chemoresistance (119). Therefore, the microbiota may induce gemcitabine resistance by shaping the PDAC intratumoral immune microenvironment. The aforementioned data markedly indicate that the microbiome can mediate therapeutic responses systematically through numerous mechanisms and that these can also be structured as the 'TIMER' mechanistic framework (120). Elucidating these mechanisms will be conducive to developing a novel targeted therapy-based microbiome.

Accurately understanding the value of synergistic methods. As described aforementioned, the microbiota can provide a novel way to enhance the efficacy and reduce the toxicity of chemotherapeutic approaches. Several strategies can be used to synergize with systemic therapy to improve efficacy, such as antibiotics, probiotics, FMT, prebiotics, diet and physical activity, by modulating the composition of the microbiome (121,122). However, future studies should accurately improve our understanding of the value of these synergistic methods.

Antibiotics. The use of antibiotics to remodel the diversity and constitution of the microbiota and alleviate toxicity have proven to be effective (123-125); however, they may also impair the response to chemotherapy. Iida *et al* (76) note that antibiotics impair oxaliplatin therapy efficacy by decreasing ROS production, which is the reason why anticancer drugs work (77) and are similarly regulated by antibiotics. The overuse of antibiotics targeting anaerobes is associated with a poor prognosis in patients with hepatocellular carcinoma who have undergone chemotherapy (126). In addition, the elimination of symbiotic bacteria increases the risk of pathogenic bacteria-induced infection (127).

Probiotics. Probiotic supplementation is beneficial for human health (128) and can also be used as an adjuvant for cancer prevention and treatment (129,130). The supernatant of *Lactobacillus plantarum* increases 5-FU chemosensitivity by inactivating Wnt/ β -catenin signaling (131). *Lactobacillus* also enhances the effects of cisplatin by upregulating interferon- γ , granzyme B and perforin-1 expression (69) and *Lactobacillus rhamnosus* can prevent 5-FU/oxaliplatin-induced intestinal injury (53,132). Irinotecan-induced intestinal injury can also be prevented by pretreatment with bacteria (133). Certain clinical studies show that combined probiotics reduce the frequency of gastrointestinal complaints during chemotherapy cycles (134,135).

In addition to probiotics, other combinations should be explored, such as metabolites or digestive enzymes. Identifying an improved combination of probiotics can significantly reduce the untoward effects of chemotherapy (136). Urolithin A, which is the main metabolite produced by the human gut microbiota, can potentiate the effects of both 5-FU and 5-dFUR on colon cancer cells (137). Probiotics supplemented with digestive enzymes can restore the gut microbial community and protect against 5-FU-induced gut dysbiosis (56).

FMT. There are few studies on FMT for improving systemic anticancer therapy. Le Bastard *et al* (138) assess the efficacy of FMT in 5-FU-induced gut dysbiosis in a mouse model. FMT ameliorates the disruption of the intestinal microbiota by significantly enriching the species with anti-inflammatory properties in mice (138). The results show that FMT has the potential to improve the resistance and toxicity induced by systemic therapy for PDAC. However, due to its uncertainties, FMT might increase the chance of infection and fecal donor selection and screening are difficult. Therefore, selective microbiota transplantation may be a better choice and additional studies should be carried out to investigate that option.

4. Conclusion

Although few of these studies have focused on PDAC, the mechanism underlying drug alterations by the microbiome may be similar. Microbiome studies provide a novel direction for the improvement of the response to systemic therapy for PDAC. A deep exploration of the mechanism and the relationship between the microbiome and systemic therapy drugs for PDAC is essential, due to the low survival rate and chemotherapeutic resistance of PDAC. In clinical practice, the combination of the microbiota and its metabolites and metabolic pathways could be used to establish a model for predicting the response to systemic chemotherapy regimens, which can be conducted flexibly and individually. During regimen cycles, the microbiota is destroyed, inducing resistance. Therefore, dynamic monitoring of the gut microbiota and timely adjustment of the regimen or restoration of the composition of the microbiome through the use of cooperative strategies may prove beneficial. Admittedly, the model and detection of the microbiome composition of patients should be fast, robust and inexpensive. In addition, mechanistic studies of the microbiome could provide novel targeted therapies or synergetic schemes to establish personalized medicine for

each patient. In conclusion, the relationship and main mechanism between the microbiome and drugs for PDAC treatment were outlined in the present review and certain directions for future research were proposed.

Acknowledgements

Not applicable.

Funding

This study was supported by Sichuan Science and Technology Program (grant no. 2021YFS0234).

Availability of data and materials

Data sharing is not applicable to this article, as no data sets were generated or analyzed during the current study.

Authors' contributions

BT conceived and supervised the work. XH, ML and SH researched data and contributed equally to discussion of content, XH and ML wrote the manuscript. All authors reviewed and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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