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## Crosstalk between gut microbiota and COVID-19 impacts pancreatic cancer progression

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### Abstract

Pancreatic cancer (PC) is one of the most common causes of cancer-associated death worldwide, with a low rate of 5-year survival. Currently, the pathogenesis of PC is complicated, with no efficient therapy. Coronavirus disease 2019 (COVID-19) disease caused by severe acute respiratory syndrome coronavirus 2 further exacerbates the challenge of patients with PC. The alteration of gut microbiota caused by COVID-19 infection may impact PC progression in patients *via* immune regulation. The expression of inflammatory immune mediators such as interleukin (IL)-6, IL-8, and IL-10 has been found to increase in both PC and COVID-19 patients, which is associated with the disease severity and prognostic outcome. Gut microbiome serves as a critical connector between viral infection and PC. It can regulate host systemic immune response and impact the efficacy of immunotherapy. Here, we first demonstrated the features of inflammatory cytokines in both diseases and their impact on disease outcomes. Then, we demonstrated the importance of immunotherapeutic strategies. This includes the immune modulation that targets a single or dual receptors using a single agent or their combinations for the treatment of PC in patients who get infected with COVID-19. Additionally, we explored the possibility of managing the disease by regulating gut microbiome. Overall, modulation of the lung-gut-pancreases axis can boost anti-cancer immunotherapy and reduce adverse prognostic outcomes.

**Key Words:** COVID-19; SARS-CoV-2; Gut microbiota; Pancreatic cancer; Interleukin-6; Interleukin-8; Interleukin-10; Monoclonal antibodies; Modulatory treatment

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**Core Tip:** Pancreatic cancer (PC) is a leading cause of cancer-associated death worldwide. Currently, the pathogenesis of this disease is complicated without efficient therapy. Coronavirus disease 2019 (COVID-19) disease exacerbates the challenge of PC patients. The gut microbiome serves as a critical connector between viral infection and PC through the regulation of host systemic immune response. Therefore, by targeting the lung-gut-pancreas axis, we can modulate both cytokine storm and inflammation in patients with PC and COVID-19 infection.

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## INTRODUCTION

Pancreatic cancer (PC) is the leading cause of cancer-associated death globally, only about 9% of patients can survive more than 5 years according to the American Cancer Society's report (February 2021)[1,2]. The major type of PC is pancreatic ductal adenocarcinoma (PDAC), about 90% of all PC cases[3], which is caused by tumor growth of the cell that lines in the pancreatic ducts[4,5]. The pancreatic ducts play a key role in the transportation of pancreas-produced digestive enzymes to the duodenum (the proximal part of the small intestine). This process is critical for digestion[6,7]. Although the pathogenesis of PC is still under intensive investigation, there is a lot of progress has been made. Several factors such as smoking, diabetes, alcohol abuse, and dietary factors have been identified as contributors. They are closely associated with cancer development. Those are the potential factors that contribute to the higher risk of PC development[8-11].

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus infection may worsen the disease progression in patients with PC. Here, we summarize the role of gut microbiota, which functions as an important connector for COVID-19 and PC.

## PC AND ITS CLOSE ASSOCIATION WITH GUT MICROBIOME

Accumulating studies showed that gut microbiome plays a vital role in pancreatic diseases, including gut microbiota and their components such as CpG-rich DNAs. For example, dysbiosis of gut microbiota can accelerate the severity of chronic pancreatitis. Chronic pancreatitis is considered as one of the contributing factors that cause PC[12,13]. In addition, the profiles of gut microbiota have been shown to be altered in PC patients compared to that in the cohort controls. However, several studies showed that the treatment with probiotics[14] or synbiotics[15] did not show a significant effect on patients with acute pancreatitis. Recently, a remarkable finding was made by Riquelme *et al*[16], which showed the diversity and composition of gut microbiome were associated with the survival time of patients with PDAC. PDAC patients who survived more than 5 years showed a higher diversity of gut microbiome. In addition, they found the microbiome contains an intra-tumoral unique microbiome component, including *Pseudoxanthomonas*, *Streptomyces*, *Saccharopolyspora*, and *Bacillus clausii*, compared to the cohorts who survived less than 5 years[16]. This study also shows that the associated immune signatures are different between the two cohorts. There was a significant positive correlation between CD3<sup>+</sup>, CD8<sup>+</sup>, and GzmB<sup>+</sup> cells tissue densities and the overall survival of PDAC patients. The causation role of gut microbiome in the survival of PC patients was further verified. The corresponding microbiome from the patient was colonized into the tumor-bearing germ-free mice, respectively. The result showed a similar pattern of survival between the colonized mice and the clinical patient. In detail, the tumor-bearing germ-free mice that were colonized with the microbiome originated from the long-term survival patients had long-term survival. The mice received microbiome that from the short-term survival patients displayed a short-term survival[16]. In addition, tumor-bearing mice who received fecal microbial transplantation (FMT) from long survival patients have a higher number of CD8<sup>+</sup> T cells CD8<sup>+</sup> T cells, specifically activated T cells (CD8<sup>+</sup>/IFN $\gamma$ <sup>+</sup> T cells) in the tumor environment, whereas mice that received FMT from short term survival patients had increased infiltration of CD4<sup>+</sup>FOXP3<sup>+</sup> regulatory T cells (Tregs) and myeloid-derived suppressor cells in the tumor. In summary, the abovementioned examples demonstrate that gut microbiome contributes a significant role in the pathogenesis of PC and tumor progression through the mechanism of microbial components modulation and associated change of immune activation. Therefore, alteration of gut microbiome could affect the severity and prognostic outcome of PC.

## COVID-19 INFECTION ALTERNATED GUT MICROBIOME

In the pandemic era of COVID-19, the situation may be even worse for PC patients who get infected by SARS-CoV-2. Besides the major respiratory syndrome, gastrointestinal symptoms such as diarrhea and abdominal pain were also observed, reported, and identified in patients infected with COVID-19[17,18]. In addition, the isolation and detection of SARS-CoV-2 viruses from the gut enterocytes and fecal samples in COVID-19 patients indicated that infection of viruses influences the intestine system. The viruses in the intestine could impact gut microbiome[19]. Notably, angiotensin-converting enzyme II (ACE2) is the important binding receptor for SARS-CoV-2 viruses binding to the host. The ACE2 is broadly expressed in the epithelial cells in the lung, gastrointestinal, vascular endothelial cells, brain, *etc.* The presence of those ACE2 receptors increases the susceptibility of the abovementioned cells to the virus infection[20]. Meanwhile, the other critical enzyme for viral binding and entering into the cell is transmembrane protease serine 2 (TMPRSS2), which is also expressed in the small intestinal epithelial cells[18]. Thus, the presence and expression of ACE2 and TMPRSS2 in gastrointestinal epithelial cells provide a physiologic foundation for the interaction between COVID-19 and gut microbiome. What's more, studies have demonstrated that the components of gut microbiota are closely associated with the expression level of ACE2. For example, some *Bacteroides* species, such as *Bacteroides dorei* and *Bacteroides thetaiotaomicron*, have the properties of downregulating the ACE2 expression in the murine model[21]. This indicates that gut microbiome plays an important role in the expression level of ACE2. Because of that, gut microbiome is important to host susceptibility and immunity during the COVID-19 infection.

In addition, serving as the binding receptor of coronavirus, ACE2 also plays an essential role in the expression of neutral amino acid transporters. Those transporters can be found in the intestine and the compositions of the gut[22]. The alteration of gut microbiome in COVID-19 patients has been investigated by several studies[23-25]. The results from those studies showed that there were an increased level of opportunistic pathogens and a decreased level of commensal symbionts in the gut of COVID-19 patients. Those commensal symbionts possess the properties of the immunomodulatory function. Butyrate-producing microbiota such as *Faecalibacterium prausnitzii* (*F. prausnitzii*) (phylum Firmicutes), *Eubacterium rectale* (phylum Firmicutes), and *Bifidobacterium adolescentis* (phylum Actinobacteria) are well-known as immunomodulators. They play important role in maintaining intestinal health with anti-inflammatory function[24]. For example, the *F. prausnitzii* has been demonstrated to display anti-inflammatory function and induce polarization of dendritic cells and the priming of interleukin (IL)-10-producing T cells in the human colon. A study showed a significant association between the decreased level of *F. prausnitzii* and the severity of COVID-19 disease in the patients[23,24].

Taken all together, the presence of ACE2 and TMPRSS2 in intestinal epithelium cells is the physiological foundation. The impact of gut microbiome on the expression level of ACE2 provided evidence of their association. Plus, the alteration of gut microbiome happened during COVID-19 occurrence. Additionally, the severity of the COVID-19 was shown to be associated with the level of a certain microbiome. All those above-mentioned aspects illustrate that the gut microbiome is closely associated with COVID-19. Gut microbiome could be the connection for the pancreatic patients infected with SARS-CoV-2[26], through the gut-pancreas axis.

## PANCREATIC INJURY AND ABNORMALITIES IN COVID-19 PATIENTS

Interestingly, pancreatic injury and abnormalities have been reported in SARS-CoV-2 infected patients. However, the mechanism including the cause-effect needs to be further investigated[27]. The statistical analysis was performed for 1378 SARS-CoV-2 infected patients (including both males and females) ranging from mild to severe infection. The result showed that the increased levels of enzyme amylase in serum were significantly related to the COVID-19 severity and the prognosis of infection[28]. Elevated serum enzyme amylase level is also known as an indicator of pancreatic-associated diseases, such as acute pancreatitis and pancreas inflammation[29]. The serum amylase comes from both salivary amylase and pancreatic amylase. The gut serves as a linkage. Through the gut-blood barrier and peritoneal blood barrier, the salivary amylase and the pancreatic amylase are absorbed into the blood vessel. Therefore, both pancreatic inflammation and leakage or damage of gut epithelium integrity can cause an increase in serum amylase[30,31]. Previous analysis of 351 metastatic PC patients showed that there was a positive association between the increased plasma amylase level and negative prognostic outcomes for PC[32]. Thus, the observation of elevated serum amylase levels from the COVID-19 patients highlights the importance to investigate the crosstalk between the SARS-CoV-2 infection, the pancreatic-associated inflammation, and the gut-associated inflammation.

Another analytical study was conducted by a group using the COVID-19 family database (SARS-CoV, SARS-dORF6, SARS-BatSRBD, and influenza A virus subtype H1N1 included) due to the lack of COVID-19 patient databases. They found an upregulated expression level of several genes, such as *CREB1*, *PTEN*, *SMAD3*, and *CASP3* genes in COVID-19 patients. Meanwhile, those genes were also highly expressed in PC. Scientists proposed that there was a potential risk of development of pancreatic severity followed by the SARS-CoV-2 infection[33]. In addition to the data analysis, oncological

treatment procedures should be optimized to provide better outcomes for pancreatic patients in the COVID-19 pandemic era, minimizing morbidity and mortality[34,35].

## LUNG-GUT-PANCREAS AXIS

Gut microbiota plays an essential role in host health and disease through various mechanisms[36,37]. (1) Gut microbiota serves as an extensive metabolic repertoire to help the absorption of nutrition and to provide an energy source to maintain the host homeostasis and health; (2) Gut microbiota plays a crucial role in drug metabolism under the disease condition to facilitate the drug uptake, distribution, absorption, metabolism, excretion, and toxicity modulation; (3) Gut microbiota plays an important role in fighting against infection from bacteria and viruses; and (4) Gut microbiome contributes to maintaining homeostasis and reducing the dysbiosis caused by variable factors from both the endogenous and exogenous antigens. The gut microbiome plays the aforementioned functions through colonization resistance, immunomodulation, and metabolism.

Gut microbiota serves as a central connection between different organs to maintain the balance of the host system[38-40]. The gut-lung axis and gut-pancreas axis are related to each other *via* lymphatics, circulation system, immunomodulatory, *etc.* (Figure 1). Diseases such as SARS-CoV-2 virus infection can cause dysbiosis or gut microbiota alteration through inflammation mediators; meanwhile, pancreas diseases such as PC also can lead to the dysbiosis of gut microbiota. That was mediated by pancreatic hormone (*e.g.*, insulin, glucagon) and digestive enzyme. Similarly, the change or disruption of the stability or equilibrium of gut microbiota also can lead to various severity of the disease. This is contributed by the immunomodulators (*e.g.*, inflammatory cytokines) or bacterial metabolites [*e.g.*, short-chain fatty acids (SCFAs)]. As demonstrated and highlighted by the above-mentioned paragraphs, the alteration of gut microbiota in both COVID-19 and PC patients showed a decreased level of *F. prausnitzii* and *E. rectale*. Both are known as commensal symbionts. They are also known as butyrate-producing microbiota with important immunomodulatory properties in the host[41,42].

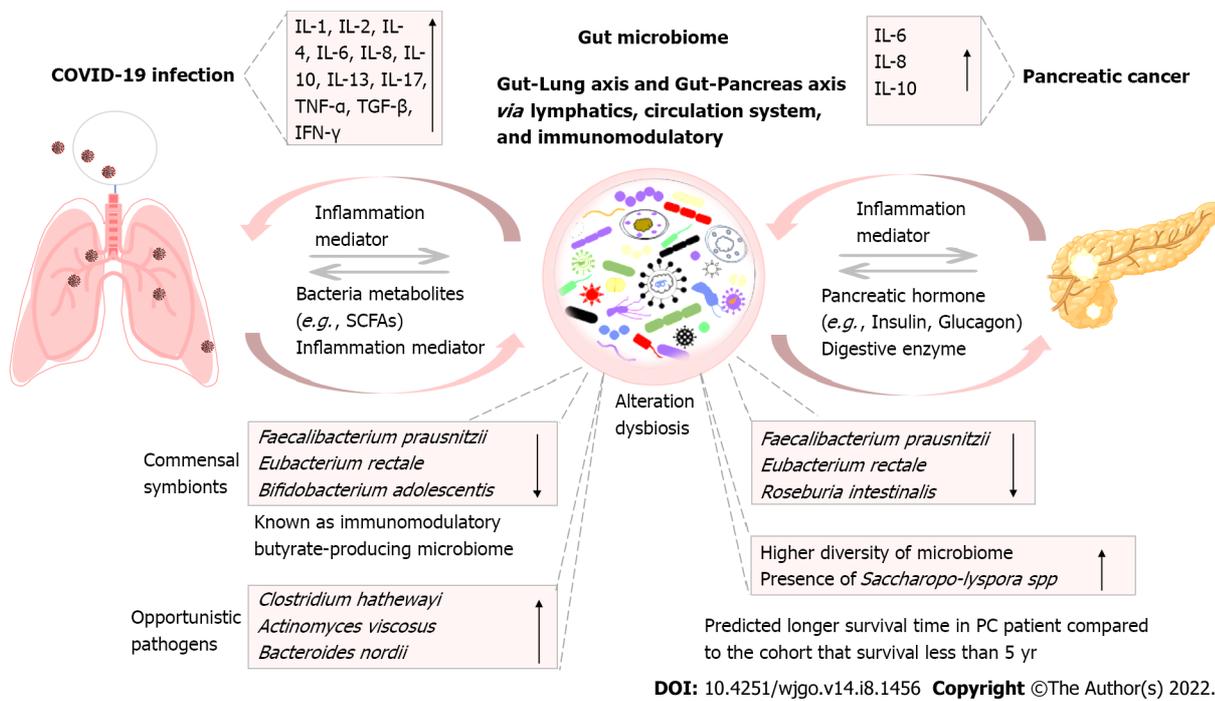
In summary, the host acts as a whole system to fight against disease and to maintain homeostasis and health condition. Therefore, it is essential to better understand the disease features such as the underlying mechanism, the immune response, the outcome of prognosis, and their associations with each other. For example, the alteration of some factors in one disease may complicate the another newly occurred disease. The altered microenvironment may cause an adverse influence on the therapeutic efficacy. Especially, caution should be taken, when it is needed to treat both the initial disease and a newly emerging disease in the same patient.

Here, we focus on the case of SARS-CoV-2 infection in PC patients. By investigating the association, correlation, and underlying mechanism, an optimized therapeutic option could be developed to better facilitate the prevention of both diseases. For PC and COVID-19, an immune response is a critical factor that influences the severity of the disease and prognostic outcome. The microenvironment in PC and the change of associated immune profile may positively/negatively influence the severity of COVID-19 in patients, and *vice versa*. Gut microbiome, as a mediator between those two diseases, needs to be further explored. This exploration could be considered from the perspective of improving the host systemic immune response and promoting treatment efficacy for both diseases. In the following discussion, we will focus on the commonality of the immune mediator in both disease and immunotherapy treatment strategies. That includes the single target and dual targets of immune mediators using a single agent or combination therapy.

## COVID-19 INFECTION INFLUENCES THE SEVERITY OF PC VIA IMMUNE MODULATION

The change of immune profile due to the SARS-CoV-2 infection could impact the severity of PC patients. A study has demonstrated that the increased levels of inflammatory cytokines are detected in the serum of COVID-19 patients compared with that in normal controls, such as increased levels of ILs (IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, IL-13, IL-17), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), transforming growth factor- $\beta$ , interferon-gamma (IFN- $\gamma$ )[43-46]. In PC, higher serum levels of IL-6, IL-8, and IL-10 are strongly associated with the progression of cancer. They are the prediction of poor prognostic outcomes of PC[47]. Thus, the increased levels of IL-6, IL-8, and IL-10 derived from SARS-CoV-2 infection may further complicate the tumor microenvironment of PC patients.

IL-6 was found as an essential factor that promotes the progression of PC. One study illustrated that the depletion of IL-6 abrogated PC progression regardless of the existence of oncogenic Kras (Kirsten rat sarcoma 2 viral oncogene homolog). The study showed that IL-6 is necessary for activation of the reactive oxygen species detoxification program during PC progression[48]. In addition, IL-6 regulates inflammatory response and results in carcinogenesis. Thus, the increasing level of IL-6 in COVID-19 patients has a negative influence on the disease severity of PC patients. Notably, IL-6 serves as a biomarker for predicting the overall severity of the COVID-19 disease[49]. Taken together, the coronavirus infection may cause an even worse situation or poor prognostic outcome for PC patients



**Figure 1** The gut-lung axis and gut-pancreas axis connect the interaction of lung infection with pancreatic cancer, via altering gut microbiota, systemic inflammation, and immune responses. COVID-19: Coronavirus disease 2019; IL: Interleukin; TGF- $\beta$ : Transforming growth factor- $\beta$ ; IFN: Interferon; TNF: Tumor necrosis factor; SCFA: Short-chain fatty acid; PC: Pancreatic cancer.

due to the increased level of IL-6.

IL-8, a neutrophil chemoattractant cytokine with pro-inflammatory function, is broadly produced by monocytes/macrophages[50], smooth muscle cells[51], epithelial cell[52], endothelial cells[53], and other cell types[54]. A study showed that a high serum level of IL-8 was detected in PC patients. That was strongly associated with a higher level of IL-6. Additionally, a higher level of IL-8 showed a significant correlation with a shorter survival time of PC patients ( $P < 0.001$ , correlation coefficient value -0.414) [47], which indicated that IL-8 could be one of the important biomarkers for the prediction of prognostic outcome in patients with PC. In vivo study showed that nude mice implanted with tumor tissues from the PC patients with higher serum levels of IL-8 grow tumors faster than the mice implanted with the tumor tissues from the patients with a lower level of serum IL-8[55]. Thus, a higher level of IL-8 serves as a predictor of the worse prognostic outcome of PC. Notably, during the SARS-CoV-2 infection, a remarkably higher level of serum IL-8 was also confirmed by several studies from COVID-9 patients[44, 56]. In a study that includes 40 COVID-19 patients, the result showed there was a significantly higher level of IL-8 in non-survival patients compared with that in survival patients. This result suggested an association between IL-8 Levels and the fatal outcome of COVID-19 disease[57]. Another study showed that the IL-8 displayed a better correlation with the clinical score of COVID-19 progression compared to IL-6. The study compared the IL-8 and the IL-6 at different time points. This indicated a possibility of using IL-8 as a biomarker to define disease status[56]. Therefore, IL-8 plays a pivotal role in both PC and COVID-19, especially for PC patients infected with SARS-CoV-2.

IL-10, a controversial immunoregulatory cytokine. Up to date, studies have reported that IL-10 displays both tumor-promoting and anti-tumor functions in cancer. Meanwhile, IL-10 also plays a complicated role in viral infection[58-60]. The elevated IL-10 in the serum of COVID-19 patients has been identified and it showed a close association with the severity of the COVID-19 disease[43,61,62].

Overall, the increased levels of inflammatory cytokines IL-6, IL-8, and IL-10 that resulted from the COVID-19 infection can facilitate the progression of acute pancreatitis. It further promotes PC progression in the patients[43,63]. Thus, it is important to consider immunotherapy as one of the treatment strategies for PC patients who encounter viral infections. Due to the complicated immune response and the commonality of the elevated levels of IL-6, IL-8, and IL-10 in both patients with COVID-19 or PC, or both, the immune mediators for a single target or dual targets could be used as a therapeutic treatment. The treatment agents could also include a single agent and the combination treatments to better improve therapeutic outcomes.

## CLINICAL TREATMENT FOR COVID-19 BY BLOCKADE OF IL-6 AND/OR IL-8 SIGNALING

An anti-inflammatory therapeutic strategy plays an important role in combating viral infections including SARS-CoV-2 infection. Targeting pro-inflammatory cytokines or non-cytokines can be chosen based on their highly elevated levels that are associated with the severity of the disease in patients, as well as the association with prognostic results[64,65]. For instance, targeting IL-6 is an attractive therapeutic option due to its critical role in COVID-19. That has been investigated by multiple studies and was mentioned above[66,67]. Treatment options for blocking IL-6/IL-6 receptors in COVID-19 include monoclonal antibodies and small molecules. Based on the mechanism, they can be divided into three categories: (1) Anti-IL-6 receptor monoclonal antibodies such as Tocilizumab and Sarilumab; (2) Anti-IL-6 monoclonal antibodies such as Siltuximab; and (3) Small molecules such as Furosemide[68-70].

### **Anti-IL-6 monoclonal antibodies**

Multiple clinical trials have been conducted to date with the status of either completed or in progress at different phases. Here, we selected some examples and summarized them in detail in a table (Table 1).

### **Small molecules are targeted to inhibit IL-6 and TNF- $\alpha$**

Compared to the IL-6 monoclonal antibody that specifically targeted the inflammatory cytokine IL-6, a small molecule has the potential advantage of expanding the targeting range. The treatment targets of the small molecule can be expanded to a broad range for therapeutic efficacy. A preclinical study that aimed to explore the treatment of using small molecules for SARS-CoV-2 infection, was conducted using *in silico* screening method and molecular simulation. As a result, a potential small molecule, Furosemide, was found to have the function of inhibiting both IL-6 and TNF- $\alpha$ . In addition, this inhibiting function was verified by *in vitro* experiment assay. Encouragingly, more investigation and evaluation are needed to screen the small molecules with the properties of dual targets such as Furosemide for COVID-19 treatment[71,72].

### **IL-8 neutralization**

The clinical trial of investigation on the effect of using BMS-986253 (neutralization of inflammatory cytokine IL-8) to treat the COVID-19 patients has been approved for recruiting. The investigation is currently ongoing (Phase 2, NCT04347226).

### **Treatment for PC by blockage of IL-6 and/or IL-8 signaling**

For PC, anti-inflammatory therapy has also been investigated in many studies, including both monotherapy and combinational treatments to improve the efficacy. For instance, an *in vitro* study showed that combinational treatment by blocking both IL-6 (Bazedoxifene) and IL-8 (SCH527123) signaling pathways displayed an enhanced effect on the reduction of cell viability and migration of PC cells[73]. Clinical trials are ongoing to evaluate the treatment efficacy of siltuximab and spartalizumab, such as trials NCT04191421 and NCT04812808 (<https://clinicaltrials.gov>, accessed on 03/10/2022). The combinational treatment with anti-IL-6R and anti-programmed death 1 (PD-L1)-blocking antibodies showed significant antitumor activity at *in vitro* cell culture. *In vivo* study, this combinational treatment improved therapeutic results and extended the survival time of mice with PC compared to controls[74].

It is worthy to point out that there are some treatments in pre-clinical and clinical studies, such as Tocilizumab[75-79], Sarilumab[80-82], Siltuximab[83,84], and others (Table 1). These above-mentioned treatments are either specifically for PC patients or specifically for COVID-19 patients. Less data is available related to the investigation of the treatment efficacy in SARS-CoV-2-infected PC patients. This shed light on the importance of investigating or documenting the clinical data in the field related to COVID-19 treatment options or strategies in PC patients.

## FURTHER EXPLORATION OF THE IMPACT OF GUT MICROBIOME ON CYTOKINE SECRETION TO ENHANCE THE TREATMENT EFFICACY

Cytokine storm in COVID-19 and inflammatory cytokines in the pancreatic tumor microenvironment are important factors that exacerbate the disease severity. In addition to directly targeting viruses and tumor cells, the exploration of clinical treatments to reduce the inflammation by targeting interleukins such as IL-6 and IL-8 is also required.

Meanwhile, as illustrated early in this paper, gut microbiome reciprocally impacts the severity of PC and SARS-CoV-2 infection. On one hand, the alteration of gut microbiota in COVID-19 may increase the severity of PC. On the other hand, the alteration of gut microbiota resulting from the PC disease could exacerbate the COVID-19 symptoms, increase the susceptibility to the infection, and influence the recovery process due to the weakened immune response. The reciprocal influence of COVID-19 and PC *via* the lung-gut-pancreas axis might be mediated by metabolites and immune modulators. Therefore, the modulation of the gut microbiome could provide a better microenvironment. The enhanced

**Table 1 Clinical and pre-clinical studies in coronavirus disease 2019 and pancreatic cancer**

Disease	Antibody/drug	Target	Title	ClinicalTrials.gov identifier	Ref.
COVID-19	Tocilizumab	IL-6 receptor	Efficacy of Tocilizumab on Patients With COVID-19	NCT04356937	[75]
COVID-19	Tocilizumab	IL-6 receptor	A Study to Investigate Intravenous Tocilizumab in Participants with Moderate to Severe COVID-19 Pneumonia	NCT04363736	[76, 77]
COVID-19	Tocilizumab	IL-6 receptor	RECOVERY Trial: Open-Label RCT of Tocilizumab and Usual Care in Hospitalized Patients With COVID-19	NCT04381936	[78, 79]
COVID-19	Sarilumab	IL-6 receptor	Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19	NCT04315298	[80, 81]
COVID-19	Sarilumab	IL-6 receptor	Sarilumab COVID-19	NCT04327388	[82]
COVID-19	Siltuximab	IL-6	An Observational Study of the Use of Siltuximab (SYLVANT) in Patients Diagnosed With COVID-19 Infection Who Have Developed Serious Respiratory Complications (SISCO)	NCT04322188	[83]
COVID-19	Siltuximab	IL-6	Treatment of COVID-19 Patients with Anti-interleukin Drugs (COV-AID)	NCT04330638	[84]
COVID-19	Clazakizumab	IL-6	Study for the Use of the IL-6 Inhibitor Clazakizumab in Patients with Life-threatening COVID-19 Infection	NCT04381052	None
COVID-19	Clazakizumab	IL-6	Clazakizumab (Anti-IL-6 Monoclonal) Compared to Placebo for COVID-19	NCT04348500	None
COVID-19	Clazakizumab	IL-6	A Randomized Placebo-controlled Safety and Dose-finding Study for the Use of the IL-6 Inhibitor Clazakizumab in Patients with Life-threatening COVID-19 Infection	NCT04343989	None
COVID-19	Furosemide	IL-6 and TNF- $\alpha$	Furosemide as Supportive Therapy for COVID-19 Respiratory Failure	NCT04588792	[72]
COVID-19	BMS-986253	IL-8	Anti-IL-8 for Patients With COVID-19	NCT04347226	None
Pancreatic cancer	Siltuximab	IL-6	Siltuximab and Spartalizumab in Patients with Metastatic Pancreatic Cancer	NCT04191421	None
Pancreatic cancer	Bazedoxifene	IL-6	Bazedoxifene as a Concomitant Treatment of Patients with Metastatic Pancreatic Adenocarcinoma (BAZE)	NCT04812808	None
Pancreatic cancer	Bazedoxifene and Navarixin (SCH527123)	IL-6 and IL-8	Blocking IL-6 and IL-8 Signaling Inhibits Cell Viability, Colony-forming Activity, and Cell Migration in Human Triple-negative Breast Cancer and Pancreatic Cancer Cells	Pre-clinical research	None
Pancreatic cancer	Antibody	IL-6 and PD-L1	IL-6 and PD-L1 antibody blockade combination therapy reduces tumor progression in murine models of pancreatic cancer	Pre-clinical research	None
Pancreatic cancer	Oncolytic vaccinia virus armed with IL-10	IL-10	A new role of IL-10 in enhancing the antitumor efficacy of oncolytic vaccinia virus for the treatment of pancreatic cancer	Pre-clinical research	None

COVID-19: Coronavirus disease 2019; IL: Interleukin; TNF: Tumor necrosis factor; PD-L1: Programmed death 1.

microenvironment is beneficial to promote the treatment efficacy through the modulation of microbiota-associated immunity. There are several strategies to modulate the microbiome. For instance, (1) Supplementing with beneficial microbiota such as butyrate-producing bacteria *F. prausnitzii* with anti-inflammatory and immunoregulatory functions. The decreased abundance of *F. prausnitzii* was found to be associated with a negative prognosis in both COVID-19 and PC patients; and (2) Modulating the gut microbiota to improve the colonization resistance *via* immune modulator or metabolism. This could assist to boost the systemic immune resilience and reduce microbial dysbiosis-induced inflammation. For example, commensal bacteria *Bifidobacterium longum* displayed protective properties against the influenza viruses in a mouse model[85]. Using the fecal microbiota transfer method, scientists transferred the antigen-experienced microbiota from wild mice into germ-free mice. The result showed the enhanced resistance to lethal influenza A virus infection and increased survival in a mouse model [86]. Those studies demonstrated the important roles of gut microbiota conferred against viral infection. Therefore, more investigation is needed to explore and improve host resistance to viruses. In particular, it is necessary to explore the strategy from the perspective of creating a favored gut microbial environment that is beneficial to the host immune response during viral clearance, disease progression, and treatment efficacy.

From the clinical perspective, accumulating studies and clinical outcomes demonstrated that the gut microbiome influences the response of immune therapy in cancer patients[87-89]. A previous study found that the microbiome, such as *Faecalibacterium* and *Ruminococcaceae*, positively correlated with the better outcome of the anti-PD-1 treatment for melanoma cancer[90]. The gut microbiome also influences the efficacy of PD-1 blockade immunotherapy in epithelial tumors. The low level of commensal bacteria *Akkermansia muciniphila* (*A. muciniphila*) was identified in the non-response patient. Supplemented with *A. muciniphila* could alter the nonresponse response to PD-1 blockade treatment. The underlying mechanism is through the modulation of IL-12[91]. The enriched commensal bacteria *F. prausnitzii* showed close association with a better response to immune therapy. The underlying mechanism is related to the metabolite, SCFA butyrate. *F. prausnitzii* could produce butyrate through metabolism. The concentration of butyrate (high or low) could modulate the production of IFN- $\gamma$  and IL-10[92,93], respectively. Most recently, a report showed that gut microbiome *Bacteroides*, *Ruminococcus*, and *Faecalibacterium* were associated with the clinical outcome of anti-CD19 CAR T cell treatment[94]. The above-mentioned examples better illustrated that the microbiome has an impact on the clinical treatment efficacy in cancer patients.

It is worth noticing that the clinical data on PC treatment and the influence of the gut microbiome is limited. However, regardless of what kind of cancer, there are commonalities in immunotherapy between cancers. Plus, there are some shared similarities in the underlying mechanism between cancers. Thereby, the clinical investigation of microbiome influence on the response of PC is urgently needed.

Currently, there is limited clinical data on the relationship between treatment efficacy of COVID-19 and gut microbiome. One reason is that only the infected patients who have critical emergency conditions can be hospitalized due to the pandemic. At this critical stage, life-saving medical care is needed. Another reason is that the medicine for COVID-19 is under development. For clinical trials, most efforts were focused on the evaluation of the effectiveness on a large scale. The effort is limited, especially, for further examining the influence of the associated factors on treatment efficacy.

However, there is accumulating data on the association between the COVID-19 vaccination and gut microbiome. Several clinical trials are ongoing. For example, some clinical trials (NCT04884776 and NCT04798677; Clinicaltrials.gov) are focusing on the investigation of gut microbiome influence on COVID-19 vaccination efficacy[95]. In addition, most recently, a report better demonstrated the association between the gut microbiome and clinical vaccination efficacy. This investigation was performed using shotgun metagenomic sequencing in the vaccinated population. They discovered that a gut microbiome community that facilitates the carbohydrate metabolism is beneficial to the efficacy of COVID-19 vaccination. In people with a higher richness of *Bifidobacterium adolescentis*, a higher level of neutralizing antibodies was produced when vaccinated with CoronaVac. People with enriched microbiome such as *Roseburia faecis* showed close association with the BNT162b2 vaccination efficacy [96]. Therefore, the commensal microbiome was correlated with the vaccine-induced neutralization effect. Collectively, gut microbiome plays an important role in host response to the virus (vaccination or treatment). More clinical studies are desired.

The cancer treatment normally causes a weakened immune system in patients. This increases the patient risk and susceptibility to virus infection. Upon the infection, the disease severity could dramatically increase. The management of the clinical care and treatment strategy is a big challenge[97]. Moreover, the application of the COVID-19 vaccine to a cancer patient is another big challenge. The efficacy and safety need to be well-evaluated. Recently, the first safety-related clinical case was reported. The case showed that a cancer patient got the Vaccine-induced thrombotic thrombocytopenia after mRNA-1273 vaccination[98]. In summary, strategies need to be explored to enhance the clinical treatment efficacy for cancer. Meanwhile, exploration should be made to improve the vaccination and treatment efficacy for virus infection. Gut microbiome, serve as an important component in both cancer treatment outcome and vaccination response. Modulation of the gut microbiome could be a potential option to be investigated. The change of microbial environment in the initial disease should be taken into consideration. That consideration helps develop the best options for health care and treatment.

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## CONCLUSION

Collectively, the reciprocal influence between COVID-19 and PC disease through the cross-link of gut microbiota may pave the way for the exploration of therapeutic options. For instance, the options include the modulation of gut microbiota *via* dietary intervention, the supplementation of beneficial bacteria, or intake of favored metabolites. Those options can be used to enhance the systemic immune response to battle against both viruses and tumors. The connection of diseases such as COVID-19 and PC through gut microbiota should be investigated to better prepare for a newly emerged disease in the future. Additionally, the efficacy of using synergistic treatment also needs to be explored and evaluated. For instance, it is important to explore the treatment efficacy of using dual agents compared to a single agent. The treatment strategy that aims to target multiple factors in the disease is also favored. For example, in addition to directly controlling the pathogen (*e.g.* virus), it is also critical to control the inflammation-caused damage (*e.g.* Cytokine storm). Therefore, the exploitation of diverse treatment

strategies is urgently needed, especially, for patients with complex disease situations.

## FOOTNOTES

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