Delta University Scientific Journal
Journal home page: https://dusj.journals.ekb.eg

Review article

Insights into Gut Microbiota and Pancreatic Cancer: A Review

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ABSTRACT

Pancreatic cancer is one of the major causes of cancer-related death worldwide and has a poor prognosis as pancreatic cancer usually shows little or no symptoms until it has advanced and spread. Therefore, most cases (up to 80 percent) are diagnosed at later, more difficult-to-treat stages. Currently, treatment relies on surgical resection and adjuvant therapies. Recent advances in biomedical research have highlighted the potential role of gut microbiota in the pathogenesis and progression of various cancers, including pancreatic cancer. The gut microbiota plays a crucial role in metabolism and immunomodulation. Emerging evidence suggests that the gut microbiota influences the metabolism of chemotherapeutic drugs and the tumor microenvironment, potentially affecting the efficacy of chemotherapy and immunotherapy for pancreatic cancer. In this review, we discuss the key connections between pancreatic cancer, the gut microbiota, and therapeutic effectiveness. We also highlight the promising potential of modifying the gut microbiota to enhance clinical outcomes for pancreatic cancer.

Keywords: *Gut microbiota; Pancreatic cancer; Chemotherapy; Immunotherapy*

Introduction

Pancreatic cancer remains one of the most lethal malignancies, characterized by a high mortality rate and limited therapeutic options. Recent advances in biomedical research have highlighted the potential role of gut microbiota in the pathogenesis and progression of various cancers, including pancreatic cancer. The gut microbiota, a complex community of microorganisms residing in the gastrointestinal tract, is known to influence numerous physiological processes, including immune function, metabolism, and inflammation. Emerging evidence suggests that dysbiosis, or the imbalance of the gut microbiota, may contribute to the development and progression of various cancer diseases including; pancreatic cancer. Dysbiosis has been demonstrated to have a role in the genesis of carcinomas of the colon, stomach, oesophagus, pancreas, larynx, breast, and gallbladder. This is intimately linked to host inflammation, which increases susceptibility to infections and is both a cause and an aggravation of microbial dysbiosis (Sheflin et al., 2014).

Dysbiosis could associated with the emersion of pancreatic cancer via different mechanisms involving immune modulation, inflammation, and metabolic alterations (Pushalkar et al., 2018; Riquelme et al., 2019). Recent studies suggest that human pancreatic illnesses, including pancreatitis and pancreatic ductal adenocarcinoma (PDAC), are significantly influenced by the gut flora. Various bacterial metabolites can regulate the immune system, treatment resistance, and pancreatic carcinogenesis. Intertumoral bacteria have also been identified in the tumor microenvironment (TME) of PDAC. Understanding the altered efficacy of chemotherapeutic drugs and immunotherapies against PDAC requires investigating the interplay between host microbiota and therapeutic effectiveness (Akshintala et al., 2019). Metagenomic sequencing, quantitative polymerase chain reaction (qPCR), and 16S ribosomal RNA sequencing are standard techniques for assessing microbial communities. These methods provide a better understanding of the multifunctionality of microbiota (Akshintala et al., 2019). This review aims to provide a comprehensive overview of the current understanding of the interplay between gut microbiota and pancreatic cancer, exploring the potential implications for diagnosis, prognosis, and therapeutic strategies. By elucidating these connections, we seek to pave the way for innovative approaches in the prevention and treatment of pancreatic cancer.

1. Therapeutic dilemma of pancreatic cancer

The primary challenge in chemotherapy and immunotherapy for advanced-stage pancreatic ductal adenocarcinoma (PDAC) is the variable effectiveness of the treatments. The desmoplastic stroma environment inhibits intertumoral

blood flow and therapeutic delivery, while hypoxia and somatic cancer mutations further contribute to treatment resistance (Chand et al., 2016). Recent discoveries have spurred clinical research on the tumor microenvironment (TME) to improve drug diffusion into tumor tissues. Unfortunately, clinical trials combining stroma-targeting drugs with gemcitabine have not improved patient survival rates in metastatic PDAC cases (Catenacci et al., 2015). Additionally, PDAC shows poor responsiveness to single doses of immune checkpoint inhibitors (ICIs) such as anti-PD-1/anti-PD-L1, anti-CTLA-4, and anti-LAG-3 (Skelton et al., 2017; Pu et al., 2019). Recent studies highlight the differences in gut microbiota between cancer patients and healthy individuals. One study revealed that while the duodenal mucosa microbiota of PDAC patients and healthy controls shared similar species, PDAC patients' duodenal samples were enriched with genera such as *Acinetobacter*, *Aquabacterium*, *Oceanobacillus*, and *Rahnella*. However, limitations remain in determining whether microbiota alterations contribute to tumor progression. The mechanisms within the tumor microenvironment of PDAC that affect therapy effectiveness are largely unclear and require further investigation. Emerging evidence suggests that gut microbiota may play a role in cancer immunomodulation and therapy, presenting novel targets for enhancing therapeutic efficacy (Maier et al., 2018).

2. Standard treatments for pancreatic cancer

2.1. **Surgery**: Surgical resection of pancreatic cancer is the mainstay of treatment for patients with non-metastatic disease. Whipple procedure is a surgical procedure that involves removing the head of the pancreas, the gallbladder, part of the stomach, part of the small intestine, and the bile duct. Enough of the pancreas is left to produce digestive juices and insulin. Another surgical intervention is the total pancreatectomy; in which the entire pancreas, part of the stomach, part of the small intestine, the common bile duct, the gallbladder, the spleen, and nearby lymph nodes are removed. Also, distal pancreatectomy is a surgical procedure to face pancreatic cancer and involves removing the body and the tail of the pancreas (Trophy et al., 2020).

2.2. Radiation therapy

Radiation therapy uses high-energy x-rays or other types of radiation to kill cancer cells (Reyngold et al., 2019).

2.3. Chemotherapy

Chemotherapy involves using drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. Chemotherapy is now the primary therapeutic option for PDAC tumors that are incurable. 2′,2′-difluorodeoxycytidine, sometimes referred to as gemcitabine, is an antimetabolite medication that prevents DNA synthesis during the S phase of the cell cycle (Sally et al., 2022).

2.4. Chemoradiotherapy

Chemoradiotherapy combines chemotherapy and radiation therapy to increase the effectiveness of both treatments (Versteijne et al.,2022).

2.5. Targeted therapy

Targeted therapy uses drugs or other substances to identify and attack specific cancer cells. Tyrosine kinase inhibitors (TKIs), such as erlotinib, block signals needed for tumors to grow and are used to treat pancreatic cancer (Kelley and Ko., 2008).

3. Human microbiota and its role in health

The human microbiota consists of organisms inhabiting and interacting with the human body, engaging in commensalistic, mutualistic, or pathogenic interactions. The human microbiome refers to the genomic content of these organisms at specific sites in the human body (Markowiak et al., 2017). Prebiotics are non-digestible food ingredients that selectively stimulate the growth and activity of beneficial bacterial species in the intestine, positively influencing host health. On the other hand, probiotics are living microorganisms that enhance gut health by modulating immune responses, increasing mucosal IgA production, and competing with pathogenic bacteria. Synbiotics combine probiotics and prebiotics to provide synergistic health benefits (Markowiak et al., 2017).

4. Microbiome and pancreatic ductal adenocarcinoma (PDAC)

4.1. Prognostic value of microbiome profiles

The microbiome profile can predict patient outcomes in PDAC. A study examining 283 PDAC tumor samples found Fusobacterium species in 8.8% of the samples, associated with significantly shorter cancer-specific survival, regardless of other clinical and molecular characteristics. Additionally, microbial profiles of short-term and long-term survivors showed differences, with *Fusobacterium*, *Rothia*, and *Neisseria* enriched in short-term survival samples, linking higher microbial diversity to better outcomes (Siegel et al., 2021).

4.2. Microbial diversity and survival

Long-term PDAC survivors exhibit greater intratumoral microbiome diversity. Specific microbiome signatures, including *Pseudoxanthomonas*, *Streptomyces*, *Saccharopolyspora*, and *Bacillus clausii*, predict long-term survival (Riquelme et al., 2019). These findings suggest that microbiota diversity and composition may predict PDAC prognosis and survival, warranting further research to clarify biomarkers and resolve inconsistencies (Torres et al., 2015).

5. Influence of gut microbiota (GM) on pancreatic cancer (PC)

5.1.1. Microbial influence on outcomes

Evidence suggests GM impacts PC outcomes. Long-term PDAC survivors have higher tumor microbial diversity, with specific bacteria like *H. pylori* implicated in PC onset and progression. Bacterial translocation from the oral cavity or intestine, involving species like *Fusobacterium* spp., also links to PC (Li etal., 2020).

5.1.2. Intrapancreatic microbiota

Research reveals a significant increase in intrapancreatic bactibilia in PDAC compared to normal pancreatic tissue, challenging the sterile pancreas assumption (Wei et al., 2019). Studies of pancreatic cyst fluid microbiota indicate certain taxa may contribute to pancreatic neoplasia, with bacterial composition, rather than abundance, correlating with carcinogenesis (Figure 1). *Enterococcus* and *Enterobacter* species in bile suggest potential pathways for GM transport to pancreatic tissue (Maekawa et al., 2018).

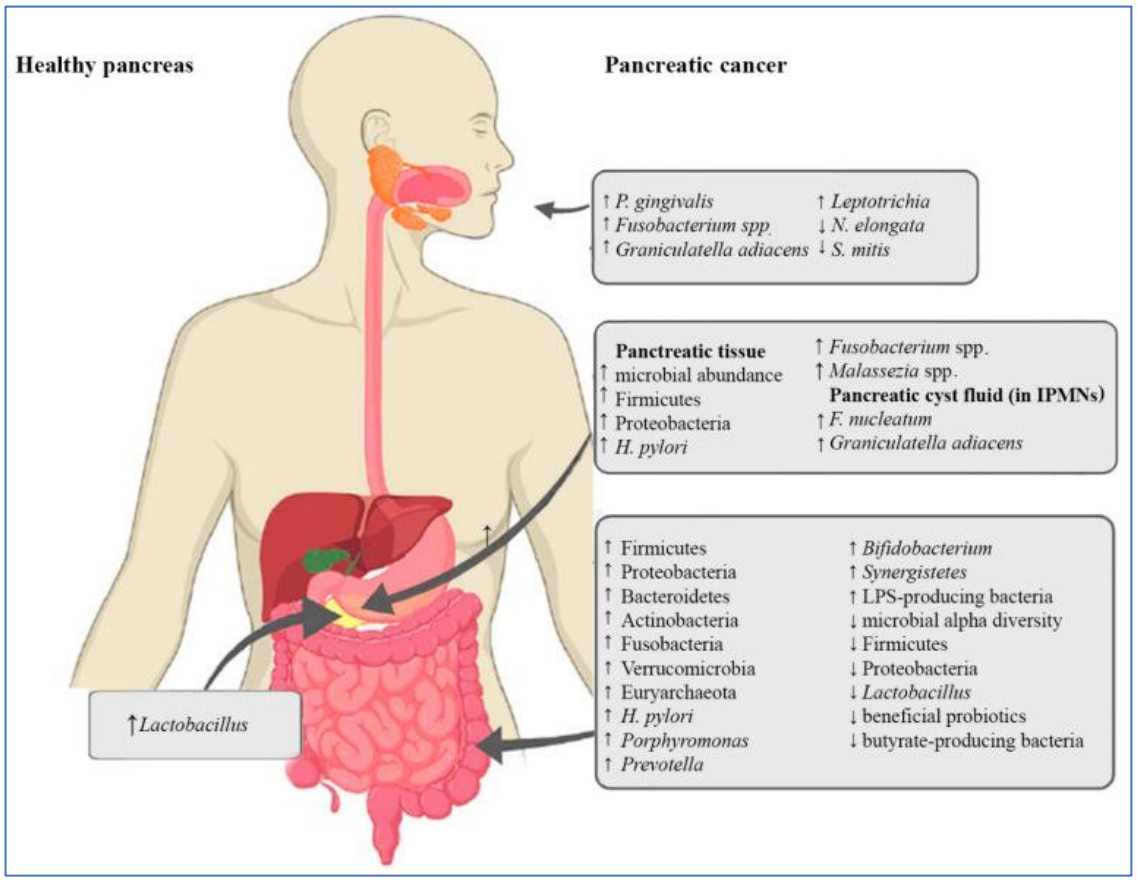

Figure1. Changes in oral, pancreatic, and intestinal microbiota in pancreatic cancer (PC). ↑ denotes an increase, while ↓ denotes a decrease (Sammallahti et al., 2021).

6. Microbiota-mediated immunoregulation

The symbiotic relationship between the human body and microorganisms relies on the interplay between immune cells and microbes. The immune system plays a crucial role in modulating host-microbe symbiosis by influencing the microbiota. Conversely, the gut microbiota (GM) is essential for the maturation and ongoing education of the host immune system, and it helps maintain homeostasis in the face of immune system imbalances, such as those seen in tumor development. The innate immune system employs a limited number of germline-encoded pattern recognition receptors (PRRs), which identify pathogen-associated molecular patterns (PAMPs) associated with microorganisms (Fulde and Hornef, 2014).

Toll-like receptors (TLRs) are key mediators of gut inflammatory pathways that bridge innate and adaptive immunity. Numerous studies have highlighted the impact of TLR gene polymorphisms on the susceptibility to colorectal cancer (CRC). Furthermore, activated TLRs play a significant role in inflammation propagation and tumor progression, particularly in response to microbiota-derived products like lipoproteins. Besides recognizing microbial molecular patterns, TLRs can also respond to inflammation- or damage-related molecular patterns (DAMPs), activating proinflammatory pathways that lead to cytokine production and may contribute to cancer initiation and progression. For instance, blocking the activation of TLR7 has shown promise in preventing pancreatic carcinogenesis (Zambirinis et al., 2015).

Pancreatic ductal adenocarcinoma (PDAC), an aggressive malignancy, interacts with stromal cells to create a highly inflammatory tumor microenvironment that fosters tumor growth and invasiveness. The precise nature of the interaction between the stroma and the tumor remains unclear. Innate immunity and environmental cues converge via TLRs, initiating proinflammatory signaling cascades. Our hypothesis posits that carcinogenesis relies on TLR7 signaling, supported by findings showing increased TLR7 expression in both epithelial and stromal compartments in human and mouse pancreatic cancer. Activation of TLR7 significantly promoted tumor development in a mouse model of pancreatic cancer, whereas blocking TLR7 offered protection from carcinogenesis. This underscores the potential therapeutic value of targeting TLR7. Therefore, TLR7 activation exacerbates pancreatic cancer by inducing stromal inflammation, as the progression of pancreatic carcinogenesis relies on stromal expansion. In support of this, our research revealed that mice deficient in TLR7 specifically within their inflammatory cells were protected from neoplastic development (Ochi et al., 2012).

7. Microbiota metabolites in pancreatic cancer

The microbiota and their metabolites play crucial roles in both physiological and pathological processes within the body, including cell proliferation, differentiation, apoptosis, tumor development, and aggressiveness. A diet high in fat and energy facilitates the absorption of harmful microbiota metabolites, such as bacterial lipopolysaccharide (LPS), into the bloodstream. This is partly because the microbiota influence carbohydrate metabolism and the production of short-chain fatty acids (SCFAs), which can damage the tight junctions of the intestinal mucosal epithelium, allowing bacterial endotoxins to enter the circulation (Wang et al., 2019).

Clinical findings indicate an increased presence of LPS-producing bacteria in the intestines of pancreatic cancer (PC) patients. Additionally, PC tissues primarily contain gram-negative bacteria, such as Proteobacteria and Bacteroidetes, which have LPS. Notably, many LPS-containing bacteria are found in the microenvironment of PC tumors. LPS is a specific agonist that activates the Toll-like receptor 4 (TLR4) signaling pathway in immune cells. Research has shown that TLR4 is also highly expressed in various cancer cells, including PC cells, and may enhance PC cell proliferation and invasion. Recent experimental data suggest that disruption of the intestinal barrier leads to elevated circulating LPS and increased LPS deposition in tumor tissues. Initially, LPS can significantly infiltrate CD3+ and CD8+ T cells, inhibiting tumor growth, but prolonged exposure results in T cell depletion. Furthermore, LPS upregulates programmed cell death ligand 1 (PD-L1) and induces the depletion and apoptosis of tumor-infiltrating lymphocytes (TILs), promoting cancer immune evasion (Figure 2). Additionally, TLR activation can inactivate several tumor suppressor proteins (such as p16, p21, p27, p53, pRb, PTEN, and MAP2K4), induce STAT3 activation, promote epithelial-mesenchymal transition (EMT), PC cell migration, and oncogene-induced senescence (Yin et al., 2021).

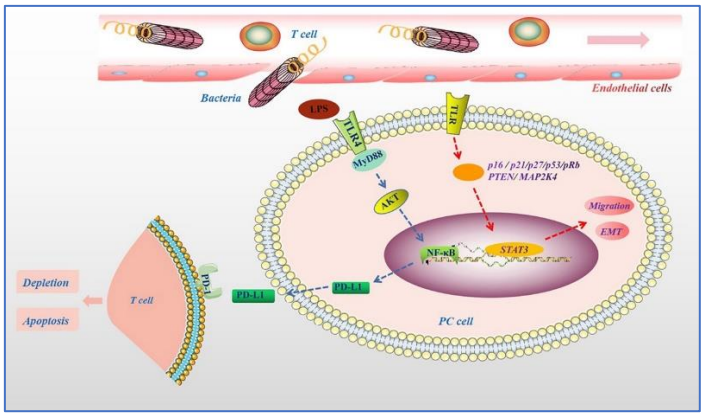

Figure 2. Pathogenic molecular mechanisms of microbial metabolites in pancreatic cancer (PC). Microbial components like LPS in the pancreatic tumor microenvironment (TME) increase PD-L1 expression via the

TLR4/MyD88/AKT/NF-κB signaling pathway and lead to the depletion and apoptosis of tumor-infiltrating lymphocytes (TILs). TLR activation can disrupt various tumor suppressor proteins, including p16, p21, p27, p53, pRb, PTEN, and MAP2K4, resulting in STAT3 activation, enhanced migration, and epithelial-mesenchymal transition (EMT) (Chen et al., 2022).

8. Microbiota driven Chronic inflammation

Pancreatic cancer is closely linked to inflammation, which is considered a defining characteristic of the disease. Research has shown that mutations in the Kras gene, which plays a crucial role in cell signaling pathways controlling cell growth, maturation, and death, are significantly influenced by gut microbiota (GM) alterations and inflammation. Although Kras is frequently mutated in 90% of pancreatic cancer cases, inflammation driven by lipopolysaccharides (LPS) (Figure 3) is still required for Kras activation (Daniluk et al., 2012). The activated Kras then triggers elements of the nuclear factor kappa B (NF-κB) pathway, further accelerating carcinogenesis (Huang et al., 2014).

Additionally, studies have demonstrated that chronic inflammation in pancreatic tissue can cause insulin-producing endocrine cells to acquire oncogenic Kras mutations, leading to pancreatic ductal adenocarcinoma (PDAC). Periodontal inflammations, such as gingivitis and periodontitis, are also believed to contribute to systemic inflammation (Chang et al., 2016). *Porphyromonas gingivalis*, the most common oral microbe associated with periodontal disease, has been implicated in this process (Ahn et al., 2012).

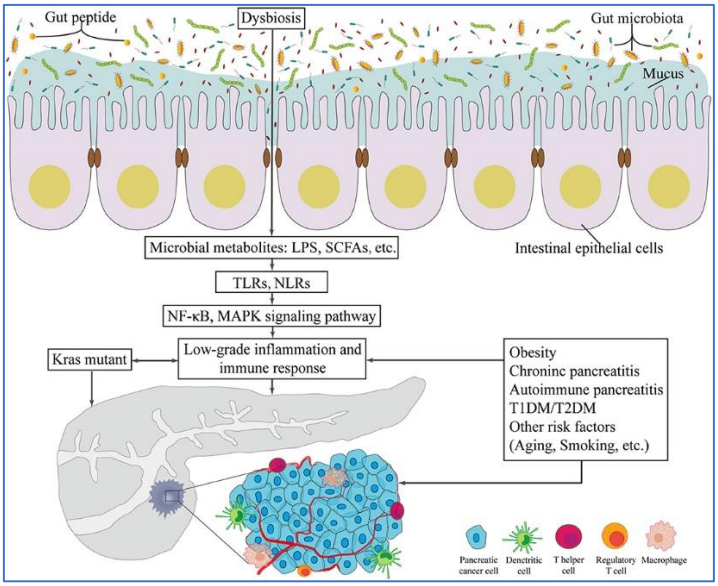

Figure 3. The potential carcinogenic roles of gut microbiota in pancreatic cancer. Disruptions in gut microbiota contribute to various changes linked to pancreatic cancer. Locally, it reduces the thickness of intestinal mucus and

the levels of gut peptides. Bacterial metabolites, such as LPS and SCFAs, can infiltrate and cause low-grade inflammation and immune responses through TLR and NLR, activating the NF-κB and MAPK signaling pathways. Additionally, risk factors for pancreatic cancer provide new avenues for exploring the connection between gut microbiota and pancreatic cancer. Abbreviations: LPS, lipopolysaccharides; SCFA, short-chain fatty acids; TLR, Toll-like receptor; NLR, Nod-like receptor; NF-κB, nuclear factor kappa B; MAPK, mitogen-activated protein kinase; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus (Li et al., 2020).

9. Microbiota and chemotherapy

Previous evidence has demonstrated that both cancer cells and their associated tumor microenvironment (TME) components participate in cancer development and treatment adaptation. Recent studies have revealed that the gut microbiota may contribute to the efficacy of conventional chemotherapeutic agents through drug metabolism, biotransformation, and immune regulation. The gut microbiota has been shown to have beneficial effects on chemotherapy both in vitro and in vivo. For instance, the clinical potential for microbial therapeutic use was highlighted by the synergistic effect of *Salmonella typhimurium* in mouse models of pancreatic ductal adenocarcinoma (PDAC) treated with gemcitabine and bevacizumab (Hiroshima Y. et al., 2014).

Additionally, the culture supernatant of *Lactobacillus plantarum* was found to improve the chemosensitivity of colorectal cancer (CRC) cells to 5-fluorouracil (5-FU) by inhibiting the formation of cancer stem-like cells (An J. and Ha E.M., 2016). Although gemcitabine remains the first-line treatment for advanced pancreatic cancer, its benefits on patient survival are often suboptimal. One reason may be that the microbiota undermines the antitumor properties of gemcitabine. Geller et al. (2017) demonstrated that most microorganisms associated with pancreatic tumors are Gammaproteobacteria, including *Enterobacter* and *Pseudomonas*, which can produce cytidine deaminase (CDD). This enzyme promotes the metabolism of gemcitabine into its inactive form, 2',2'-difluorodeoxyuridine, leading to gemcitabine degradation and resistance. The combination of gemcitabine with antibiotics was found to be more effective than gemcitabine alone (Corty et al., 2020).

In tumor-bearing mouse models treated with cyclophosphamide (CTX), the gut microbiota promoted an adaptive immune response to restore antitumor efficacy. CD8+ T cells play critical roles in the adaptive antitumor immune response. The commensal bacterial species *Enterococcus hirae* and *Barnesiella intestinihominis* were identified as key players in CTX-induced immunomodulation, which altered the TME and enhanced anticancer cytotoxic T lymphocyte (CTL) responses. These bacteria were capable of partially restoring host T cell responses and improving the therapeutic efficacy of CTX and other alkylating agents (Cogdill A.P. et al., 2018).

Collectively, these findings elucidate the complex influences of the gut microbiota on both exogenous drugs and endogenous responses. Chemotherapeutics can induce efficacy, alter the microbiota, and cause toxicity, presenting challenges in achieving optimal anticancer effects and reducing side effects through gut microbiota manipulation (Kurita A. et al., 2011)

Table 1. Preclinical and clinical studies on the microbiota and therapeutic efficacy for solid pancreatic tumors in the past decade.

Therapeutic drugs or targets	Microbiota ormicrobial intervention	Efficacy	Mechanisms	Reference
Gemcitabine	*Gammaproteo bacteria*	Nonbeneficial	BacterialCDD inactivates gemcitabine	Geller *et al*., 2017
Cyclophosphamide	*Enterococcus hirae*	Beneficial	Translocation increases CD8/Treg ratio withintumor	Daillère *et al*., 2016
	Barnesiella intestinihominis	Beneficial	Increase IFN-γ^+ $\gamma\delta^+$ T cells within tumor	
5-Fluorouracil	*Lactobacillusplantarum*	Beneficial	Decrease cancer stem-like cells	An and Ha 2016
Gemcitabine	*Mycoplasma hyorhinis*	Nonbeneficial	Bacterial CDD and nucleoside phosphorylase decrease cytostaticactivity	Vande *et al*., 2014
Oxaliplatin/cisplatin	Antibiotic treatment	Nonbeneficial	Reduce myeloid cell ROS	Iida *et al*., 2013
Cyclophosphamide	*Lactobacillus johnsonii, Lactobacillus murinus, Enterococcus hirae*	Beneficial	Induce bacterial translocation, which stimulates pathogenic Th17 andmemory Th1immune responses	Viaud *et al*., 2013

10. Multicellular fungus *Aspergillus oryzae*

The multicellular fungus *Aspergillus oryzae* (*A. oryzae*) is widely used as a biotechnological tool in many countries. It plays a significant role in the food industry, particularly in the production of fermented foods such as miso (soybean paste), shoyu (soy sauce), tane-koji (seed rice malt), bean curd seasoning, and vinegar. This is due to its strong ability to produce amylase and protease, which allows it to break down proteins and various starches into sugars and amino acids (Watarai et al., 2019).

Aspergillus oryzae also positively contributes to gut microflora by serving as a favorable substrate for the growth of beneficial bacteria in the intestine, such as various *Lactobacillus* species. These beneficial bacteria compete with harmful bacteria like *E. coli* by producing bacteriocins (antimicrobial peptides) (Kim et al., 2003).

A previous investigation identified heptelidic acid as a metabolite of *A. oryzae* (Shinohara et al., 2019). A xenograft model of pancreatic cancer cells demonstrated the anti-tumor impact of heptelidic acid both in vitro and in vivo.

Heptelidic acid exerts its anti-tumor effects on pancreatic cancer cells as it passes through the intestinal mucosa (Konishi et al., 2021).

The tumor-suppressive properties of heptelidic acid in pancreatic cancer cells were validated using a Sulforhodamine B (SRB) experiment. Heptelidic acid strongly inhibited the development of SUIT-2, MIA-PaCa-II, and PANC-1 cells in a concentration-dependent manner. To assess its tumor-suppressive effects in vivo, SUIT-2 cells were implanted into mice, and heptelidic acid was administered daily into the transplanted tumor. The treatment significantly reduced tumor size (Konishi et al., 2021).

11. Probiotics and cancer treatment

Probiotics are live microorganisms that confer health benefits on the host, most frequently belonging to the lactic acid bacteria categories *Lactobacillus* spp. and *Bifidobacterium* spp..Using a mouse model of pancreatic cancer (PC) xenotransplantation, Panebianco et al. (2021) found that probiotics combined with chemotherapy can significantly increase the DNA damage in PC cells, effectively inhibit the cell cycle, induce cell apoptosis, and suppress epithelial-mesenchymal transition (EMT) of PC cells. They also help preserve the overall structure of the intestinal mucosa and increase the species richness of the intestinal microbiota, which is mainly manifested in the bacteria that produce butyrate and other beneficial short-chain fatty acids (SCFAs), such as *Eubacteriaceae*, *Ruthenibacterium*, *Faecalicatena*, *Pseudobutyrivibio*, and *Roseburia*. Additionally, probiotics restore platelet counts affected by gemcitabine (Panebianco et al., 2021).

Mice treated with gemcitabine combined with probiotics had lower levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), indicating that probiotics can enhance the effectiveness of standard chemotherapy and improve patients' tolerance to it (Chen et al., 2020). In a xenograft model, the probiotic bacteria *Lactobacillus casei* could suppress the progression of cancer cells and induce apoptosis in PC cells by activating p53 and hindering the cell cycle. The transcription factor known as the tumour suppressor p53 has developed the capacity to combine several environmental cues, such as DNA damage, viral infection, and cytokine signaling, into a single biological result that preserves regular cellular regulation. The cellular transcription program is changed by mutations in p53, which leads to dysregulation of the stress responses that typically preserve the integrity of cells and tissues (Maclaine and Hupp, 2009). Its antitumor efficacy was even better compared to a combination of 5-fluorouracil (5-FU) and cisplatin in refractory and resistant PC. Thus, the microbiota could influence the therapeutic efficacy of chemotherapeutics, and the elimination of pathogenic bacteria alongside probiotic application could enhance chemotherapeutic efficacy and improve patient tolerance to chemotherapy (Kita et al., 2020).

12. Microbiota and radiotherapy

Radiotherapy is a key treatment for pancreatic cancer (PC), especially in advanced cases. It can enhance the release and absorption of tumor-associated antigens by affecting the tumor's vascular system and chemokine environment, thereby increasing the activation of anti-tumor T cells and enhancing their penetration into the tumor (Zhu et al., 2020).

The microbiota plays a crucial role in the immunological microenvironment of PC, potentially contributing to the immune system's response to radiation by activating it. However, radiation is a double-edged sword, as it can also damage healthy tissues like bone marrow and other organs while killing tumor cells. The application of probiotics can improve the tolerance of PC patients to radiotherapy. Experimental results have shown that preparations containing probiotics such as *Lactobacillus* and *Bifidobacterium* have a protective effect against radiotherapy-induced intestinal toxicity and can significantly reduce the incidence of severe diarrhea (Zhu et al., 2020).

13. Antibiotics and chemotherapy

The combination of antibiotics and chemotherapeutics can enhance the antitumor efficacy of chemotherapeutics and help improve patient tolerance to chemotherapy. For example, Weniger et al. (2021) found that the progression-free survival (PFS) of some PC patients was not improved after adjuvant gemcitabine treatment post-surgery. Intraoperative bile cultures of these patients revealed the presence of *Klebsiella pneumoniae*, and their survival time significantly improved after quinolone treatment (Weniger et al., 2021).

14. Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) involves transplanting healthy donor bacteria back into the gut, which can be done through various techniques such as nasogastric tube, endoscope, colonoscopy, or enema (Figure 4). The method chosen often depends on the ability to place the bacteria in the terminal ileum and colon, where they likely belong. Donors are screened to ensure they do not transmit infections, similar to blood or organ donation processes, including screening for *Clostridium difficile* to prevent transmission. FMT from a healthy donor can improve dysbiosis and various disorders in patients (John et al., 2014).

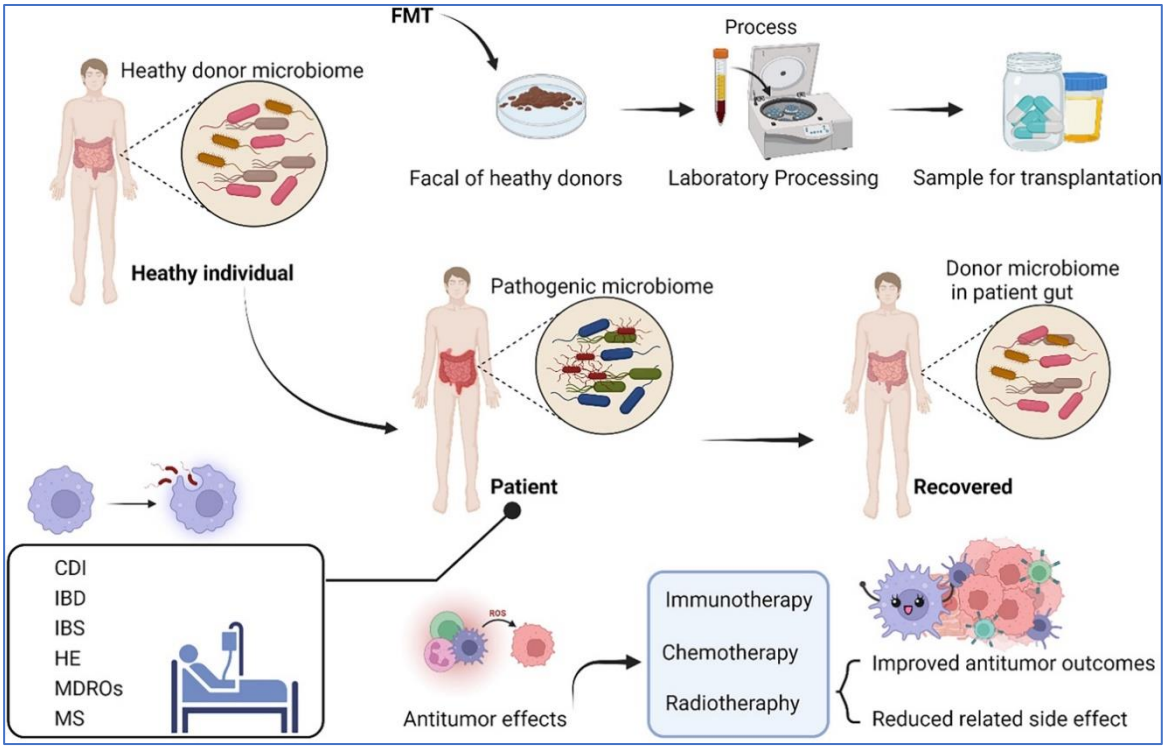

Figure 4. Fecal microbiota transplantation (FMT) from a healthy donor helps correct dysbiosis and treat various disorders in patients. FMT can be used to manage several diseases, including *Clostridioides difficile* infections (CDIs), infections with multidrug-resistant organisms (MDROs), inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and neurological disorders such as multiple sclerosis (MS), hepatic encephalopathy (HE), Parkinson's disease, and diabetic neuropathy. FMT can enhance the gut microbiome in patients with poor therapeutic responses or severe side effects. Additionally, FMT has antitumor properties and can reduce associated toxic events, especially when combined with immunotherapy, chemotherapy, or radiotherapy (Xu et al., 2022).

Conclusion

The correlation between gut microbiota and pancreatic cancer has undergone thorough scrutiny in recent years. Changes in gut microbiota have been shown to influence the development of pancreatic cancer. Microbes have the potential to impact the tumorigenic process. Interventions aimed at modifying gut microbiota, including the administration of prebiotics, probiotics, next-generation probiotics, synbiotics, and fecal microbiota transplantation, hold promise for novel therapeutic approaches in treating pancreatic cancer. Nonetheless, further clinically focused studies are warranted to validate the efficacy of these interventions.

Disclosure

The authors have no conflicts of interest to declare

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