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REVIEW

Gut microbiota and pancreatic cancer: tumorigenesis, progression, and clinical applications

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ABSTRACT Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive malignancies of the digestive system, with a 5-year survival rate of only 13%, which is largely due to late-stage diagnosis and limited therapeutic options. Emerging evidence indicates that the gut microbiota has a critical role in PDAC tumorigenesis, progression, and therapeutic response. This review comprehensively summarizes current insights into gut microbiota-PDAC interactions, highlighting microbial alterations across taxonomic, functional, and clinical dimensions. Gut dysbiosis, which is marked by depletion of beneficial species and enrichment of pathogenic taxa, contributes to carcinogenesis through chronic inflammation, immune dysregulation, and metabolic reprogramming. In particular, the loss of butyrate-producing bacteria reduces anti-inflammatory activity and weakens $CD8^+$ T cell function, thereby promoting tumor development. In addition to initiation, the gut microbiota also shapes PDAC progression through direct translocation to pancreatic tissue and systemic regulation of the tumor microenvironment (TME), influencing immune cell dynamics and fostering therapeutic resistance. Clinically, distinct microbial signatures are emerging as potential diagnostic and prognostic biomarkers. Moreover, microbiota-targeted interventions, including probiotics, synbiotics, fecal microbiota transplantation (FMT), metabolite supplementation, and dietary modulation, show promise as adjunctive therapeutic strategies. However, significant challenges remain in defining causal mechanisms and translating these findings into practice. Future research should integrate multi-omics profiling with well-designed clinical trials to delineate the gut microbiota-PDAC interaction network, guide precision microbiota-based interventions, and ultimately enable earlier detection and personalized treatment of this lethal disease.

KEYWORDS Gut microbiota; pancreatic cancer; tumorigenesis; tumor microenvironment; biomarker; microbiota-targeted therapy

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive malignancy of the digestive system that is characterized by late diagnosis, rapid progression, and poor prognosis. Most patients present with advanced or metastatic disease due to the absence of specific early symptoms, which contribute to the dismal 5-year relative survival rate of only 13%, the lowest among all cancers[1-4]. In recent years the gut microbiota has emerged as a critical factor in cancer biology with established roles in colorectal, liver, and gastric cancers, with growing evidence implicating the gut microbiota in PDAC as well[5-9].

The gut microbiota of PDAC patients differs markedly from that of healthy individuals, typically showing a depletion of beneficial taxa and enrichment of pathogenic species[10]. Moreover, microbial composition varies within PDAC subgroups, such as between males and females or between patients with metastatic and non-metastatic disease[11,12]. Mechanistically, the gut microbiota influences PDAC tumorigenesis through inflammatory cytokines and immune modulation[13]. Dysbiosis fosters a tolerogenic, immunosuppressive microenvironment that supports tumor growth during progression and metastasis[9]. In addition, gut microbes may indirectly shape disease biology by altering the composition of the tumor-associated microbiota[14].

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Although current mechanistic insights into gut microbiota-PDAC interactions remain limited, emerging findings already suggest diagnostic and therapeutic potential. This review aims to systematically summarize the evidence linking gut microbiota with PDAC tumorigenesis, progression, and clinical applications, and to address ongoing controversies, limitations, and future directions.

Overview of PDAC pathophysiology

Basic characteristics of PDAC

PDAC accounts for >90% of all pancreatic cancer cases and represents the most common and aggressive histologic subtype[15-17]. The majority of PDACs develop from microscopic pancreatic intraepithelial neoplasia (PanIN), while <10% arise from intraductal papillary mucinous neoplasms (IPMNs)[18,19]. Activating mutations in kirsten rat sarcoma viral oncogene homologue (*KRAS*) are present in >90% of patient specimens, establishing *KRAS* as the hallmark driver of PDAC[20,21]. Additional loss-of-function alterations in tumor protein p53 (*TP53*), mothers against decapentaplegic homolog 4 (*SMAD4*), and cyclin-dependent kinase inhibitor 2A (*CDKN2A*) further drive tumorigenesis[22-24]. For example, p53 dysfunction promotes genomic instability and metabolic reprogramming, *SMAD4* loss is strongly associated with poor prognosis, and *CDKN2A* deletions at the 9p21 locus contribute to immune evasion and resistance to immunotherapy[25-29].

The pancreatic tumor microenvironment (TME) is characterized by a dense desmoplastic stroma, abnormal vasculature, and a predominance of immunosuppressive cell types[4,16,17,30]. Key stromal components include cancer-associated fibroblasts (CAFs), endothelial cells, and pericytes, while the immune compartment is dominated by tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and neutrophils along with T cells, B cells, dendritic cells (DCs), and natural killer (NK) cells[31]. Interactions among neoplastic epithelial cells, stromal elements, and immune populations drive metabolic reprogramming, promote chemoresistance, and reinforce immune suppression[32-34].

Diagnosis and treatment of PDAC

The symptoms of PDAC are largely non-specific and often appear after the tumor has advanced or metastasized. Early signs frequently resemble benign conditions, while progressive disease manifests as jaundice, anorexia, and altered bowel habits[35].

Screening protocols of PDAC must prioritize the detection of lesions less than 2 cm given the association with R0 resection potential and 5-year survival rate improvement[36]. Among available biomarkers, carbohydrate antigen 19-9 (CA19-9), a cell-surface tetrasaccharide, remains the most widely used. Although also elevated in other malignancies and some benign disorders[37], CA19-9 has shown improved diagnostic performance in recent studies with a sensitivity of approximately 50% and a specificity of 99% within 6 months prior to early-stage diagnosis[38]. In parallel, liquid biopsy-based approaches are emerging as promising tools, including circulating tumor cells (CTCs), circulating tumor DNA [ctDNA] (e.g., *KRAS*, guanine nucleotide-binding protein, alpha stimulating (*GNAS*), and *TP53* mutations), microRNAs (e.g., miR-21, miR-10b, miR-30c, miR-181a, and miR-let7a), exosome profiling (e.g., exosome concentration, epithelial cell adhesion molecule (EpCAM) expression, or exosomal *KRAS* mutations), and cell-free DNA methylation signatures[39-44]. For clinical diagnosis and staging, imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI), are essential[45,46].

The cornerstone of PDAC treatment is surgical resection combined with chemotherapy. However, only 15%–20% of patients are eligible for surgery at presentation[47]. Pancreatic surgery, which often involves partial duodenectomy, profoundly affects digestive and metabolic function, underscoring the importance of comprehensive preoperative assessment[48]. For the majority of patients, systemic chemotherapy is central to management. Two regimens are widely accepted as first-line therapy in advanced disease: 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX); and the combination of gemcitabine with nab-paclitaxel[49]. Given the high risk of micro-metastases, surgery alone rarely prevents recurrences, making adjuvant chemotherapy essential[50,51]. In addition to standard modalities, recent advances in targeted and immune-based therapies are reshaping the therapeutic landscape. A major breakthrough in the treatment of PDAC has been the development of drugs directly targeting *KRAS*, a mutation present in 90% of PDAC patients and once deemed "undruggable"[52]. Immunotherapeutic approaches are also under investigation, aiming either to reprogram immunosuppressive cells within the TME or to enhance antitumor immunity through adoptive transfer and activation of antigen-presenting cells and effector T cells (Teffs)[53]. These strategies, particularly strategies directed against recurrent genetic alterations, represent promising avenues to expand treatment options for this highly lethal disease[54].

Composition and function of the gut microbiota

Composition of the gut microbiota

The human gut microbiota is a highly complex ecosystem comprised of bacteria, archaea, eukaryotes, and viruses. Systematic analyses have cataloged >1,000 cultivable microbial species within the gastrointestinal tract, including 957 bacterial species, 92 eukaryotes, and 8 archaea[55]. Early culture-based studies suggested the presence of a shared "core microbiota"

across healthy adults[56]. Firmicutes and Bacteroidetes dominate at the phylum level, accounting for >90% of total abundance[57,58]. At finer taxonomic scales, major taxa include, at the class level, Bacilli, Clostridia, and Actinobacteria, among others; at the order level, Bifidobacteriales, Coriobacteriales, and Actinomycetales, among others; at the family level, Bacteroidaceae, Prevotellaceae, and Rikenellaceae, among others; and at the genus level, *Bifidobacterium*, *Collinsella*, and *Propionibacterium*, among others[55]. In addition, methanogenic archaea (notably *Methanobrevibacter smithii*), eukaryotic species (chiefly yeasts), and viral populations (mainly bacteriophages) are integral to the gut ecosystem[56].

The gut microbiota can be stratified into three enterotypes based on function that is dominated by different genera: *Bacteroides* (enterotype 1); *Prevotella* (enterotype 2); and *Ruminococcus* (enterotype 3)[59]. Microbial distribution also varies along the gastrointestinal tract. The colon harbors the highest density of microbes, which is dominated by Firmicutes and Bacteroidetes[58]. In contrast, the small intestine has a lower microbial biomass that is characterized mainly by *Clostridium*, *Escherichia*, *Bacteroides*, *Streptococcus*, and *Veillonella*, reflecting the rapid luminal transit and exposure to antimicrobial secretions[60].

Substantial interindividual variation in microbiota composition challenges the concept of a universal "core microbiota"[56]. Diet is a major determinant and strongly influences enterotype stratification[61]. Age also drives distinct shifts. Specifically, the neonatal microbiota is enriched in *Bifidobacterium*, whereas elderly individuals have a higher representation of *Bacteroides*[62,63]. Geographic and ethnic factors further shape microbial ecology, as shown by large cohort studies across nine Chinese provinces and seven ethnic groups, highlighting pronounced differences between urban and rural populations[63].

Core functions of the gut microbiota

The gut microbiota performs essential physiologic functions, including neuroregulation, nutrient metabolism, immune modulation, and maintenance of barrier integrity (**Figure 1**).

Neuroregulation

The gut microbiota communicates bidirectionally with the enteric nervous system (ENS) and central nervous system (CNS). Microbial signals influence brain function through vagus nerve activation and *via* lipophilic bacterial metabolites capable of crossing the blood-brain barrier (BBB), such as short-chain fatty acids (SCFAs), which may directly influence the brain by enhancing BBB integrity, modulating neurotransmission, affecting levels of neurotrophic factors, and promoting memory consolidation[64]. In addition, the microbiota may regulate tryptophan-degrading enzymes in the kynurenine pathway and directly utilize serotonin, thereby reducing tryptophan availability and serotonin synthesis, ultimately affecting the development of both the central and peripheral nervous systems[65].

Homeostasis of the gut microbiota is closely linked to host neuroregulation. Enterochromaffin (EC) cells secrete serotonin locally, which acts directly on gut microbiota, particularly spore-forming taxa. Moreover, EC cells can also regulate activities of the nervous system, such as visceral pain and anxiety[66]. With respect to distal regulation, sympathetic nerves influence norepinephrine secretion, modulate barrier function to affect microbial colonization, and directly release norepinephrine into the intestinal lumen, where sympathetic nerves interact with gut microbiota[67].

Nutrient metabolism

Microbial communities possess broad catabolic capacity, enabling the breakdown of otherwise indigestible dietary substrates. Glycoside hydrolases degrade cellulose and hemicellulose[68]. Bacterial proteases convert undigested proteins into bioactive peptides and amino acids[69]. Bile salt hydrolases deconjugate unabsorbed bile salts, altering lipid metabolism[70,71]. Other microbial transformations include the conversion of choline into trimethylamine (TMA), which is absorbed and further metabolized systemically[72]. Some commensals, such as *Anaerobutyricum hallii*, *Roseburia faecis*, and *Anaerostipes caccae*, also contribute to vitamin B12 biosynthesis[73].

Immune modulation

Gut microbes regulate immune homeostasis largely through the actions of SCFAs. SCFAs modulate the differentiation, recruitment, and activation of innate and adaptive immune cells, including neutrophils, DCs, macrophages, monocytes, and T cells[74]. Among the SCFAs, butyrate has strong anti-inflammatory effects that is achieved by inhibiting NF-κB signaling, suppressing pro-inflammatory cytokines (e.g., IL-12 and TNF-α), and inducing epithelial heat shock proteins (HSPs)[75-78]. Acetate modulates inflammatory responses in human monocytes *via* free fatty acid receptor 2 (FFAR2) and FFAR3 activation, while propionate has been shown to promote neutrophil apoptosis through caspase-dependent mechanisms[74,79].

Barrier maintenance

The gut microbiota is indispensable for sustaining intestinal barrier integrity[80]. Microbial communities influence the structure and composition of the mucus layer, thereby affecting the epithelial defense system[81].

Influence of environmental and lifestyle factors

Environmental and lifestyle factors shape the composition of the gut microbiota. As noted earlier, diet is a key determinant of the gut microbiota composition. A diet rich in fiber promotes the growth of beneficial bacteria, such as *Roseburia*, whereas a diet high in saturated fat and sugar may favor the expansion of microbes associated with metabolic

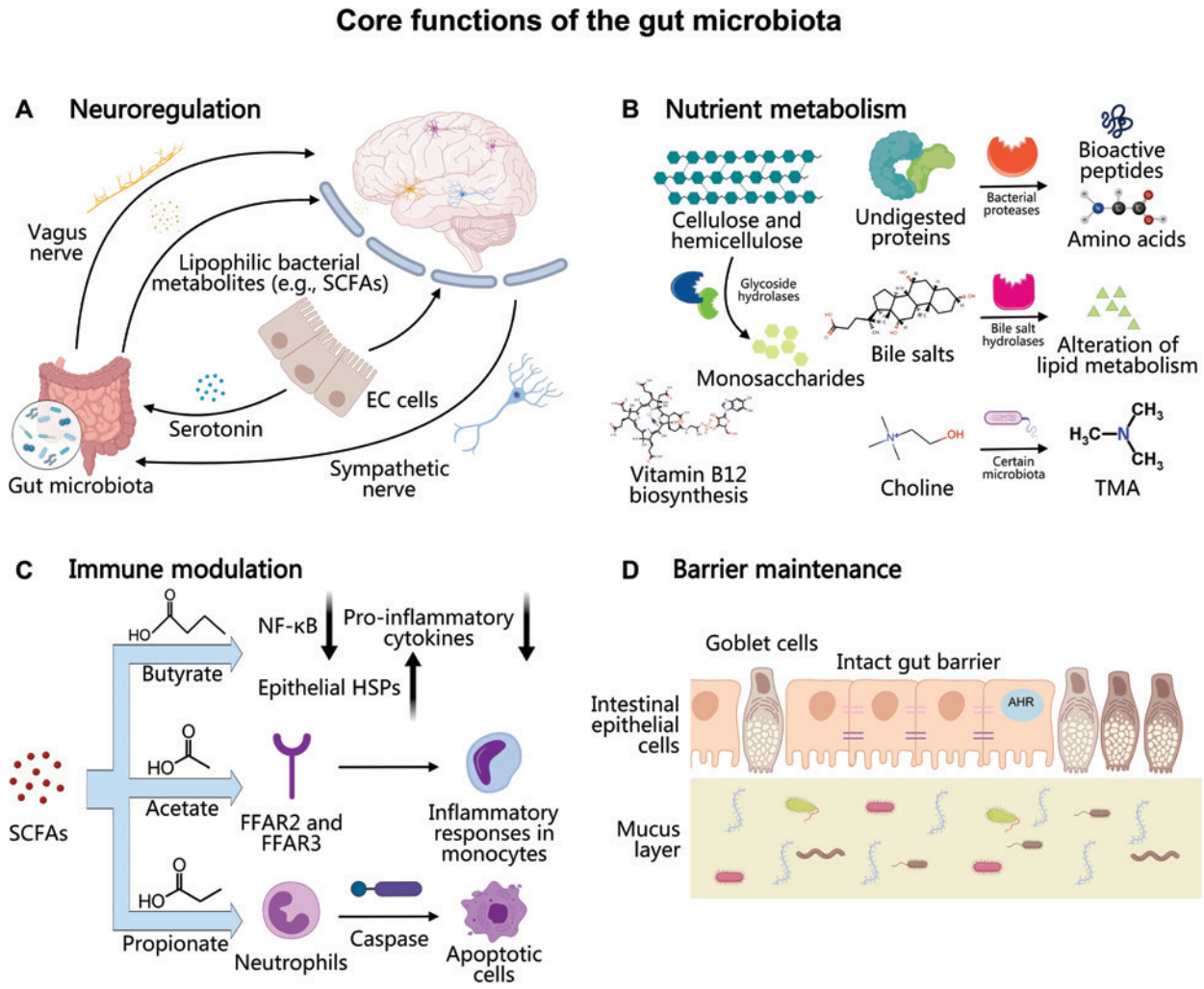


Figure 1 Core functions of the gut microbiota. (A) Neuroregulation: the gut microbiota engages in bidirectional communication with the nervous system. The gut microbiota influences brain function *via* the vagus nerve or by lipophilic bacterial metabolites, like SCFAs, crossing the BBB. Conversely, the nervous system can also participate in regulating the gut microbiota: EC cells secrete serotonin, which directly affects gut microbiota, especially spore-forming taxa; EC cells also regulate neural activities, such as visceral pain and anxiety. In addition, the sympathetic nerve releases norepinephrine, which impacts microbial colonization. (B) Nutrient metabolism: the gut microbiota possesses broad catabolic capacity. Glycoside hydrolases degrade cellulose and hemicellulose into monosaccharides; bacterial proteases convert undigested proteins into bioactive peptides and amino acids; bile salt hydrolases deconjugate bile salts, thereby altering lipid metabolism. In addition, some microbiota converts choline into TMA and some commensals contribute to vitamin B12 biosynthesis. (C) Immune modulation: the gut microbiota regulates immune homeostasis primarily through SCFAs. Butyrate exerts anti-inflammatory effects by inhibiting the NF-κB signaling pathway, suppressing pro-inflammatory cytokines and inducing epithelial HSPs. Acetate modulates inflammatory responses in monocytes *via* FFAR2 and FFAR3 activation. Propionate promotes neutrophil apoptosis through caspase-dependent mechanisms, leading to the formation of apoptotic cells. (D) Barrier maintenance: the gut microbiota is indispensable for sustaining intestinal barrier integrity. The gut microbiota influences the structure and composition of the mucus layer, thereby affecting the epithelial defense system. BBB, blood-brain barrier; EC cells, enterochromaffin cells; FFAR2, free fatty acid receptor 2; FFAR3, free fatty acid receptor 3; HSPs, heat shock proteins; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; SCFAs, short-chain fatty acids; TMA, trimethylamine. The scientific illustrations in this manuscript were created with MedPeer (medpeer.cn).

conditions, such as obesity and inflammatory bowel disease (e.g., *Bilophila*)[82]. Distinct dietary patterns can even determine specific enterotypes[61]. In addition to diet, sleep also modulates the gut microbiota. For example, sleep quality is positively correlated with *Lactobacillus* abundance and altered beta diversity has been noted in patients with narcolepsy type I[83].

Moreover, physical exercise, particularly at higher intensities, enhances microbial diversity, increasing the representation of taxa involved in protein metabolism and creatine kinase synthesis[84]. Long-term alcohol consumption leads to dysbiosis, reducing the abundance of Bacteroidetes and Firmicutes, while promoting Proteobacteria and Actinobacteria; abstinence can restore intestinal barrier integrity[85]. Smoking is associated with elevated *Bacteroides-Prevotella* levels and reduced *Bifidobacterium*, whereas smoking cessation increases the abundance of key species within the Firmicutes (such as *Clostridium coccoides*, *Eubacterium rectale*, and *Clostridium leptum* subgroups) and Actinobacteria (such as high-G+C (HGC) bacteria and *Bifidobacterium*)[85].

These microbiota alterations inevitably influence intestinal cells. Complex interactions exist between microbial metabolites and host cells. Gut microbiota metabolizes bile acids into secondary bile acids, such as deoxycholic acid and lithocholic acid. Deoxycholic acid can disrupt the intestinal barrier, whereas lithocholic acid exhibits protective effects[86,87]. Intestinal serotonin can be converted by gut microbiota into indole derivatives, some of which serve as ligands for the aryl hydrocarbon receptor, thereby contributing to intestinal epithelial homeostasis[88]. Environment and lifestyle markedly affect gut microbiota composition and microbial metabolites subsequently modulate intestinal epithelial barrier stability. This finding demonstrates an indirect effect of environment and lifestyle on intestinal cells.

Environmental and lifestyle factors also influence tumor tissue biomarkers. There is a positive correlation between high-level natural radiation and CA19-9, as well as prostate-specific antigen (PSA), while aerobic exercise may have an inhibitory effect on alpha-fetoprotein (AFP) expression[89,90]. Consequently, individualized environments and habits contribute to personalized tumor biomarkers, underscoring the importance of molecular pathologic epidemiology in understanding these relationships. For example, smoking induces a mutational signature in lung cancer that is characterized by C > A transversions and is associated with *KRAS*G12C mutations in lung adenocarcinoma[91]. *KRAS* mutations influence disease progression and treatment response. While *KRAS* mutations may reduce the propensity for metastasis to the liver and pleural surface, *KRAS* mutations also decrease tumor sensitivity to bevacizumab. Notably, inhibitors targeting *KRAS*G12C mutations have been developed, offering potential prognostic benefits[92]. These observations illustrate how environment and lifestyle affect tumor biomarkers, treatment strategies, and clinical outcomes. Thus, research into personalized tumor biomarkers and related molecular pathologic epidemiology may hold clinical relevance.

Dysbiosis of gut microbiota and disease

Gut dysbiosis is increasingly recognized as a driver of complex diseases through bidirectional host-microbe interactions. For example, dysbiosis is characterized by phylum-level shifts in obesity, notably depletion of Bacteroidetes and enrichment of Firmicutes[93]. This imbalance alters SCFAs and bile acid metabolism, which contributes to weight gain and metabolic dysfunction[94]. The "obese microbiota" also demonstrates enhanced capacity for energy harvest from dietary substrates[95]. Dysbiosis marked by expansion of pathobionts and depletion of symbionts in liver disease has been linked to alcohol-associated liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), and hepatic fibrosis, conditions that predispose to hepatocellular carcinoma (HCC)[96-98]. Similarly, inflammatory bowel disease (IBD) is associated with global microbial diversity loss and pathoadaptive transitions, in which environmental triggers drive commensal microbes to adopt pathogenic functions, such as barrier disruption, mucolysis, and immune activation[99,100]. Microbial-derived metabolites further exacerbate metabolic dysregulation in type 2 diabetes mellitus (T2DM)[101].

The secretory functions of the pancreas are tightly regulated through enteroendocrine hormone-mediated crosstalk within the gut-pancreas axis. Incretin hormones, including glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1), stimulate β-cells in the islets of Langerhans to enhance insulin secretion[102]. Microbial modulation of tryptophan metabolism further amplifies GLP-1 production *via* L-tryptophan-induced activation of enteroendocrine cells[103]. Other gut-derived peptides, such as cholecystokinin (CCK), peptide YY (PYY), and oxyntomodulin (OXM), act synergistically to promote insulin release, while the newly identified enterokine famsin stimulates α-cell glucagon secretion[104,105]. In addition to metabolic regulation, the gut microbiota also influences pancreatic immune homeostasis. The migration of intestinal regulatory T cells (Tregs) to the pancreas can disturb the local Treg-to-Teff balance, undermining islet immune tolerance and accelerating type 1 diabetes (T1D) through epitope spreading and autoreactive T cell activation[106].

Mounting evidence further implicates gut dysbiosis in the initiation and progression of multiple malignancies[107]. Given the intricate metabolic and immunologic crosstalk within the gut-pancreas axis, it is increasingly plausible that microbial imbalance contributes to PDAC development. Understanding this connection may reveal novel mechanistic insights and therapeutic opportunities in PDAC pathogenesis.

The characteristic gut microbiota associated with PDAC

The gut microbiota of patients with PDAC differs markedly from healthy individuals[10]. These alterations span multiple taxonomic levels and functional dimensions, reflecting profound microbial remodeling during disease development. In

this section we summarize the compositional differences in the gut microbiota between PDAC patients and healthy controls, as well as distinct clinical or phenotypic subgroups of patients. Understanding these characteristic microbial shifts may provide deeper insights into the mechanisms underlying PDAC tumorigenesis, progression, and therapeutic response, and may facilitate the development of microbiota-based strategies for diagnosis and treatment.

Characteristic gut microbial abundance alterations in PDAC across successive taxonomic levels

This section systematically summarizes the characteristic differences in gut microbial composition between patients with PDAC and healthy individuals from phylum to species level, as shown in **Table 1**.

Phylum level

PDAC patients generally exhibit higher relative abundances of Proteobacteria and Actinobacteria, accompanied by decreased levels of Firmicutes and Bacteroidetes compared to healthy controls[10,108-110]. However, some studies have reported opposing trends in Firmicutes and Bacteroidetes abundance, suggesting that these changes may not be universal but instead reflect interpatient heterogeneity or distinct disease phenotypes[112,119]. Additional phyla, including Verrucomicrobiota, Spirochaetota, and Desulfobacterota, are also present at lower levels in PDAC patients[109].

Class level

Bacilli, Actinobacteria, and Gammaproteobacteria are commonly enriched in PDAC, whereas Bacteroidia and Clostridia are reduced[110].

Order level

Consistent with the class-level trends, the following orders are increased in PDAC patients: Coriobacteriales; Corynebacteriales; Lactobacillales; Bifidobacteriales; Enterobacteriales; Pasteurellales; and Bacillales. In contrast, Bacteroidales and Clostridiales have decreased abundance[13,108,110,111].

Family level

PDAC-associated enrichment is observed in Prevotellaceae, Streptococcaceae, Porphyromonadaceae, Bifidobacteriaceae, Lactobacillaceae, Enterobacteriaceae, Enterococcaceae, Pasteurellaceae, and Fusobacteriaceae[13,108,110,113]. In contrast, Ruminococcaceae, Piscirickettsiaceae, Phyllobacteriaceae, Lachnospiraceae, Bacteroidaceae, Veillonellaceae, Butyricicoccaceae, Erysipelotrichaceae, and Clostridiaceae are consistently depleted in patients with PDAC[108,110,112-115].

Genus level

Escherichia-Shigella, *Streptococcus*, *Staphylococcus*, *Veillonella*, *Actinomyces*, *Bifidobacterium*, *Lactobacillus*, *Enterococcus*, and *Prevotella* are frequently upregulated in PDAC patients[10,110,114-116]. Conversely, *Parasutterella*, *Faecalibaculum*, *Ileibacterium*, *Alistipes*, *Butyricicoccus*, *Roseburia*, *Bacteroides*, *Faecalibacterium*, *Blautia*, and *Ruminococcus* are reduced in patients with PDAC[109,110,114,117].

Table 1 Characteristic gut microbial abundance alterations in PDAC

Taxonomic level	Enriched in PDAC	Depleted in PDAC
Phylum[10,108-110]	Proteobacteria Actinobacteria	Firmicutes Bacteroidetes Verrucomicrobiota Spirochaetota Desulfobacterota
Class[110]	Bacilli Actinobacteria Gammaproteobacteria	Bacteroidia Clostridia
Order[13,108,110,111]	Coriobacteriales Corynebacteriales Lactobacillales Bifidobacteriales Enterobacteriales Pasteurellales Bacillales	Bacteroidales Clostridiales
Family[13,108,110,112-115]	Prevotellaceae Streptococcaceae Porphyromonadaceae Bifidobacteriaceae Lactobacillaceae Enterobacteriaceae Enterococcaceae Pasteurellaceae Fusobacteriaceae	Ruminococcaceae Piscirickettsiaceae Phyllobacteriaceae Lachnospiraceae Bacteroidaceae Veillonellaceae Butyricicoccaceae Erysipelotrichaceae Clostridiaceae
Genus[10,109,110,114-117]	*Escherichia-Shigella* *Streptococcus* *Staphylococcus* *Veillonella* *Actinomyces* *Bifidobacterium* *Lactobacillus* *Enterococcus* *Prevotella*	*Parasutterella* *Faecalibaculum* *Ileibacterium* *Alistipes* *Butyricicoccus* *Roseburia* *Bacteroides* *Faecalibacterium* *Blautia* *Ruminococcus*
Species[115,118]	*Streptococcus oralis* *Streptococcus vestibularis* *Streptococcus anginosus* *Veillonella atypica* *Veillonella parvula* *Fusobacterium nucleatum/hwasookii* *Alloscardovia omnicolens*	*Eubacterium ventriosum* *Faecalibacterium prausnitzii* *Romboutsia timonensis* *Bacteroides coprocola*

Species level

PDAC patients demonstrate higher abundances of *Streptococcus oralis*, *Streptococcus vestibularis*, *Streptococcus*

anginosus, *Veillonella atypica*, *Veillonella parvula*, *Fusobacterium nucleatum/hwasookii*, and *Alloscardovia omnicolens*, while commensals, such as *Eubacterium ventriosum*, *Faecalibacterium prausnitzii*, *Romboutsia timonensis*, and *Bacteroides coprocola*, are significantly reduced[115,118].

Together, these studies reveal substantial alterations in gut microbial abundance across successive taxonomic levels in PDAC, underscoring widespread ecologic imbalance. These compositional shifts provide an essential foundation for investigating the functional implications of gut dysbiosis in pancreatic tumorigenesis, progression, and therapeutic response.

Distinctive gut microbial signatures in PDAC across functional and clinical dimensions

While the preceding section outlined taxonomic alterations in the gut microbiota of PDAC patients, emerging evidence also revealed distinctive functional and clinical microbial signatures.

SCFAs are key microbial metabolites generated through the fermentation of dietary fiber. Among the SCFAs, butyrate has a crucial anti-inflammatory and antineoplastic role in extraintestinal cancers[120]. The gut microbiota consistently exhibits depletion of multiple butyrate-producing taxa in PDAC, including Firmicutes, Lachnospiraceae, Ruminococcaceae, Clostridiaceae, Veillonellaceae, and Butyricicoccaceae[10,109,110,112-114, 120]. This reduction likely contributes to systemic inflammation and immune dysfunction, thereby promoting tumorigenesis and progression.

Another characteristic feature of the PDAC-associated gut microbiota is the enrichment of oral-derived bacteria, notably *Streptococcus* (*Streptococcus oralis*, *Streptococcus vestibularis*, *Streptococcus anginosus*, and *Streptococcus mutans*), *Veillonella* (*Veillonella atypica* and *Veillonella parvula*), *Actinomyces*, and *Lactobacillus* (*Lactobacillus salivarius*)[110,115,121]. The expansion of these oral taxa in the intestinal microbiota of PDAC patients may be partly explained by widespread use of proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) rather than the PDAC[121-123]. A study by Matsukawa et al. supports this hypothesis. Specifically, in a comparative analysis of gut microbiota between PDAC patients with and without PPI/H2RA use *vs.* healthy controls, the only significantly enriched oral-derived species were noted in PPI/H2RA users, while other upregulated species were primarily gut-resident and exhibited substantial overlap[121]. PPIs exert a more pronounced effect than H2RAs on facilitating oral-to-gut microbial translocation, likely through indirect elevation of gastrointestinal pH or direct inhibition of acid-sensitive commensal species[123-125].

Some microbial taxa appear to exert protective, tumor-suppressive effects. Bacteroidetes, Bacteroidia, Clostridia, Bacteroidaceae, *Bacteroides*, and *Roseburia* are associated with inhibition of PanIN progression[109,126]. Functionally, these taxa are enriched in butyrate-producing species, supporting the anti-inflammatory and anti-tumorigenic properties[120,127]. In contrast, Actinobacteria, Bacilli, Lactobacillales, Lactobacillaceae, *Lactobacillus*, *Lactococcus*, *Bifidobacterium*, and *Faecalibaculum* have been linked to tumor-promoting effects, potentially through metabolic or immune-modulatory mechanisms that favor carcinogenesis[109,126].

Microbial composition also correlates with clinical prognosis in PDAC. Enrichment of *Lactobacillus*, *Alistipes*, *Phascolarctobacterium*, and *Faecalibacterium prausnitzii* is associated with favorable survival, whereas an increase in *Ruminococcus torques* correlates with poor outcomes[115,128]. Moreover, specific microbial species, such as *Lactobacillus reuteri* and *Desulfovibrio fairfieldensis*, have been shown to enhance treatment responses, suggesting that supplementation with these taxa may represent a promising adjunctive therapeutic approach[128,129].

The gut microbiota also differs markedly between metastatic and non-metastatic PDAC. At the family level, Rhodospirillaceae, Clostridiaceae, and Peptococcaceae are enriched in metastatic cases, while at the genus and species levels, *Porphyromonas* and *Odoribacter*, *Anaerostipes hadrus*, *Coprobacter secundus*, *Clostridium* spp. 619, and *Roseburia inulinivorans* display strong discriminatory power for predicting metastatic potential[12]. In addition, host-related factors, such as gender, age, and genetic background, further shape microbial composition in PDAC patients[11].

Taken together, distinctive gut microbial alterations in PDAC encompass functional downregulation, particularly of butyrate-producing, tumor-suppressive species, and pathologic enrichment, including oral-origin or tumor-promoting taxa. Some of these alterations may be influenced by external factors, such as PPI use. Collectively, these microbiotas not only bidirectionally modulate tumorigenesis but also stratify clinical outcomes related to prognosis and metastasis. Furthermore, select species, such as *L. reuteri* and *D. fairfieldensis*, highlight the emerging potential of microbiota-targeted interventions as adjunctive strategies in PDAC management.

Gut microbiota and pancreatic tumorigenesis

Gut dysbiosis as a potential driver of pancreatic tumorigenesis

Established risk factors for PDAC, including obesity, type 2 diabetes, smoking, and alcohol consumption, have all been associated with alterations in gut microbial composition[130,131]. Mounting evidence links gut dysbiosis to a wide range of metabolic and inflammatory diseases, such as obesity, type 2 diabetes, hepatic steatosis, IBD, and colorectal, hepatic, and pancreatic malignancies[132]. Notably, smoking and alcohol intake are also potent inducers of dysbiosis, further highlighting the interconnection between lifestyle factors, microbiota

imbalance, and disease pathogenesis[133,134]. In addition, gut dysbiosis has been hypothesized to promote the development of many types of cancer through systemic mechanisms and gut dysbiosis is also a potential driving factor for pancreatic tumorigenesis[135]. Together, these observations suggest that gut dysbiosis may represent a convergent mechanism through which multiple established risk factors drive pancreatic tumorigenesis.

Causal evidence supporting this association has begun to emerge. A Mendelian randomization analysis demonstrated that gut dysbiosis contributes causally to pancreatic tumorigenesis with effects mediated by immune dysregulation, specifically through naïve $CD4^+$ T cell signaling and pro-inflammatory cytokines, such as IL-6[13]. Consistent with this finding, a prospective cohort study identified elevated serum levels of trimethylamine N-oxide (TMAO), a microbial metabolite derived from dietary choline and carnitine, as a biomarker of gut dysbiosis significantly associated with increased PDAC risk[136]. Furthermore, an experimental longitudinal study revealed that dysbiosis during early pancreatic tumorigenesis enhances microbial polyamine biosynthesis pathways. These polyamines are subsequently absorbed by the host and utilized by rapidly proliferating cells, thereby promoting tumor growth and progression[137].

The preceding studies highlight potential pathophysiologic connections between gut dysbiosis and PDAC, yet the precise molecular mechanisms are not completely defined. Current evidence suggests that gut microbial imbalance can aggravate pancreatic injury and promote tumorigenesis through several interrelated pathways. First, gut dysbiosis, which is characterized by reduced *Bacteroides uniformis*, diminishes taurine production and increases colonic IL-17 release. Elevated IL-17 activates the IL-17/NF-κB signaling cascade in neutrophils, inducing the formation of neutrophil extracellular traps (NETs) that exacerbate pancreatic tissue injury[138]. Second, loss of *Lactobacillus* due to intestinal epithelial Toll-like receptor 4 (TLR4) deficiency worsens pancreatic inflammation by disrupting Paneth cell function and impairing Nod-like receptor 2 (NOD2)-dependent signaling. This TLR4 deficiency results in decreased antimicrobial peptide secretion (e.g., lysozyme and α-defensins), compromised intestinal barrier integrity, and enhanced bacterial translocation to the pancreas[139]. Third, defective gut epithelial IL-17 receptor A (IL-17RA) signaling promotes pancreatic tumorigenesis through expansion of Th17 cells and IL-17F-producing B cells. Elevated systemic IL-17 levels subsequently activate the dual oxidase 2 (DUOX2) pathway in pancreatic tumor cells, leading to excessive reactive oxygen species (ROS) generation that accelerates tumor growth and diminishes responsiveness to microbial stimuli[140].

Furthermore, studies using genetically engineered and xenograft mouse models demonstrated that gut microbiota exerts long-distance effects on pancreatic tumorigenesis, which is mediated through innate immune suppression and dysregulation of oncogenic pathways within the TME[141]. In human studies, patients with PDAC exhibit gut-associated lymphoid tissue (GALT) dysbiosis with *Klebsiella pneumoniae* enrichment, correlating with impaired B cell antigen presentation and immune checkpoint molecule (HLA-G) expression, suggesting that microbial imbalance in GALTs may contribute to systemic immune dysfunction underlying PDAC development[142].

Together, these findings underscore gut dysbiosis as a key convergent mechanism linking microbial imbalance to pancreatic injury and tumorigenesis. Through the disruption of epithelial integrity, induction of chronic inflammation, modulation of immune and oxidative stress pathways, and *via* long-distance regulation of host immunity and tumor signaling, dysbiotic gut ecosystems may create a permissive microenvironment for PDAC initiation and progression.

Gut microbial metabolite (butyrate) reduction as a potential driver of pancreatic tumorigenesis

SCFAs are the principal metabolites produced by gut microbiota through fermentation of non-digestible carbohydrates[143]. SCFAs exert broad physiologic effects locally in the intestinal tract and systemically, contributing to gut barrier integrity, glucose and lipid metabolism, immune regulation, appetite control, and protection against tumorigenesis and other chronic diseases[120,143]. Among the major SCFAs (acetate, propionate, and butyrate), butyrate is particularly important for maintaining intestinal and systemic immune homeostasis[144]. A consistent metabolic hallmark observed in patients with PDAC is the reduction of fecal and systemic butyrate levels, which likely stems from the depletion of butyrate-producing bacteria[145-147]. Given the pleiotropic anti-inflammatory, immunoregulatory, and epigenetic functions, reduced butyrate availability may contribute to pancreatic tumorigenesis[148].

Butyrate mitigates inflammation by suppressing neutrophil activation and ROS production, thereby inhibiting the formation of NETs[149]. The ROS-related nuclear factor erythroid 2-related factor 2, integrin beta 7, focal adhesion kinase (NRF2/ITGB7/FAK) axis mediates the oncogenic effects of tripartite motif-containing 2 (TRIM2) in PDAC, while NETs activate TLR4-dependent signaling in pancreatic ductal cells, upregulating IL-1β, promoting epithelial-mesenchymal transition (EMT), and driving the progression of PanIN toward malignancy[150,151]. Butyrate downregulates inflammatory mediators in macrophages, such as nitric oxide (NO), IL-6, and IL-12p40, thereby limiting pro-inflammatory responses[152]. In parallel, butyrate promotes peripheral Treg differentiation through conversed non-coding sequence 1 (CNS1) enhancer-dependent pathways, stabilizing Foxp3 protein expression *via* histone deacetylase (HDAC) inhibition-mediated acetylation. Butyrate also enhances the tolerogenic function of DCs by suppressing pro-inflammatory gene transcription[153].

Accordingly, the loss of butyrate-producing microbiota and the consequent decline in butyrate levels weaken anti-inflammatory control across multiple immune cell populations (neutrophils, macrophages, Tregs, and DCs), resulting in sustained low-grade inflammation. This chronic inflammatory state fosters epithelial transformation, enhances tumor-promoting signaling (e.g., TLR4/IL-1β/EMT axis), and ultimately accelerates pancreatic tumorigenesis.

Butyrate has a central role in sustaining effective cytotoxic T cell responses. Butyrate uncouples the tricarboxylic acid (TCA) cycle from glycolytic input in $CD8^+$ T cells, promoting oxidative phosphorylation through enhanced glutamine utilization and fatty acid oxidation. This metabolic shift supports long-term survival and memory formation of $CD8^+$ T cells[154]. Butyrate also strengthens the cytotoxic capacity by activating G protein-coupled receptor 109A (GPR109A) and the transcriptional regulator, homeodomain-only protein X (HOPX)[8]. Through combined metabolic and epigenetic reprogramming that is mediated by class I HDAC inhibition and mammalian target of rapamycin (mTOR) activation, butyrate enhances the expression of effector molecules, such as CD25, IFN-γ, and TNF-α, thereby improving antitumor efficacy in PDAC models[155]. Conversely, reduced butyrate levels impair $CD8^+$ T cell reprogramming and cytotoxicity, weakening antitumor immunity and promoting pancreatic tumorigenesis.

In addition to $CD8^+$ T cells, butyrate modulates other cell types within the pancreatic TME. Butyrate inhibits the tumor-promoting activity of $SULF1^+$ CAFs by downregulating sulfatase 1 (*SULF1*) expression through HDAC inhibition[156]. Similarly, butyrate suppresses mast cell (MC) activation by blocking degranulation *via* HDAC inhibition-mediated epigenetic silencing of FcεRI signaling components, including Bruton's tyrosine kinase (BTK), spleen tyrosine kinase (SYK), and the adaptor protein linker for activation of T cells (LAT)[157]. Given that CAFs and MCs facilitate tumor growth and fibrosis, loss of butyrate may amplify the tumor-supportive functions within the TME[158,159].

Butyrate also directly influences PDAC cells by regulating gene expression and proliferation. Butyrate inhibits TGF-α expression and protein kinase C (PKC) activity in Capan-1 cells, leading to growth arrest and cellular differentiation[160]. Butyrate induces differentiation and apoptosis through HDAC inhibition-mediated histone hyperacetylation in AsPC-1 cells, resulting in upregulation of differentiation-related genes, such as *Keratin 23* (*K23*) and *p21* wild-type p53-activated fragment 1, cyclin-dependent kinase-interacting protein 1 (*WAF1/CIP1*)[161]. Moreover, butyrate enhances ACOX1-mediated lysine crotonylation (Kcr), a post-translational modification that limits tumor cell proliferation in pancreatic tissue[126].

Taken together, gut microbiota-derived butyrate serves as a key suppressor of pancreatic tumorigenesis by integrating anti-inflammatory, immunomodulatory, and epigenetic mechanisms. Gut microbiota-derived butyrate promotes anti-tumor immunity, remodels the TME, and directly restrains tumor cell proliferation. Accordingly, butyrate depletion resulting from gut dysbiosis weakens these protective pathways and is closely associated with increased PDAC risk. The proposed mechanisms linking gut microbial imbalance, butyrate reduction, and pancreatic tumorigenesis are summarized in **Figure 2**.

The impact of gut microbiota on PDAC progression

The gut microbiota influences the progression of PDAC through direct and indirect mechanisms. *Enterococcus faecalis* and *Escherichia coli* microbes can translocate from the intestine to the pancreas, integrating into the tumor and shaping the microenvironment[162,163]. *Bifidobacterium* and Gammaproteobacteria microbes exert systemic effects, remotely modulating the pancreatic TME through immune, metabolic, or molecular pathways. Gut microbiota can alter immune cell activity within the TME, directly affect tumor cell behavior, and influence the metabolism and efficacy of chemotherapeutic agents[164-166].

Gut microbiota influences PDAC via translocation and remote regulation

The gut microbiota can affect PDAC progression through two principal mechanisms: direct translocation to the pancreas; and indirect, remote regulation of the TME.

Direct translocation to the pancreas

Pushalkar et al. used fluorescence-labeled *Escherichia coli* to demonstrate that gut bacteria can migrate to the pancreas, showing significantly higher bacterial abundance in PDAC tissues compared to normal pancreatic tissue[162]. Similarly, Ece et al. used 16S rRNA amplicon sequencing and identified intratumoral microbial taxa resembling microbial taxa present in the fecal microbiota of PDAC patients. Paired salivary and fecal metagenomic analyses further revealed that some PDAC-associated strains likely originate from the oral cavity, migrate to the gut, and subsequently reach the pancreas, suggesting an "oral-gut-pancreas" microbial transmission route. Notably, these PDAC-associated microbial taxa may complement existing biomarkers for PDAC diagnosis[118]. In addition to bacteria, gut fungi can also translocate to the pancreas and promote tumor progression by activating the complement cascade through mannose-binding lectin (MBL)-dependent pathways[167]. Although the precise mechanisms underlying microbial migration are unclear, current evidence points to gut barrier disruption followed by microbial translocation. Stefan et al. reported that bacterial translocation and infected pancreatic necrosis in acute necrotizing pancreatitis originate from the small intestine microbiota[168]. Other studies have suggested

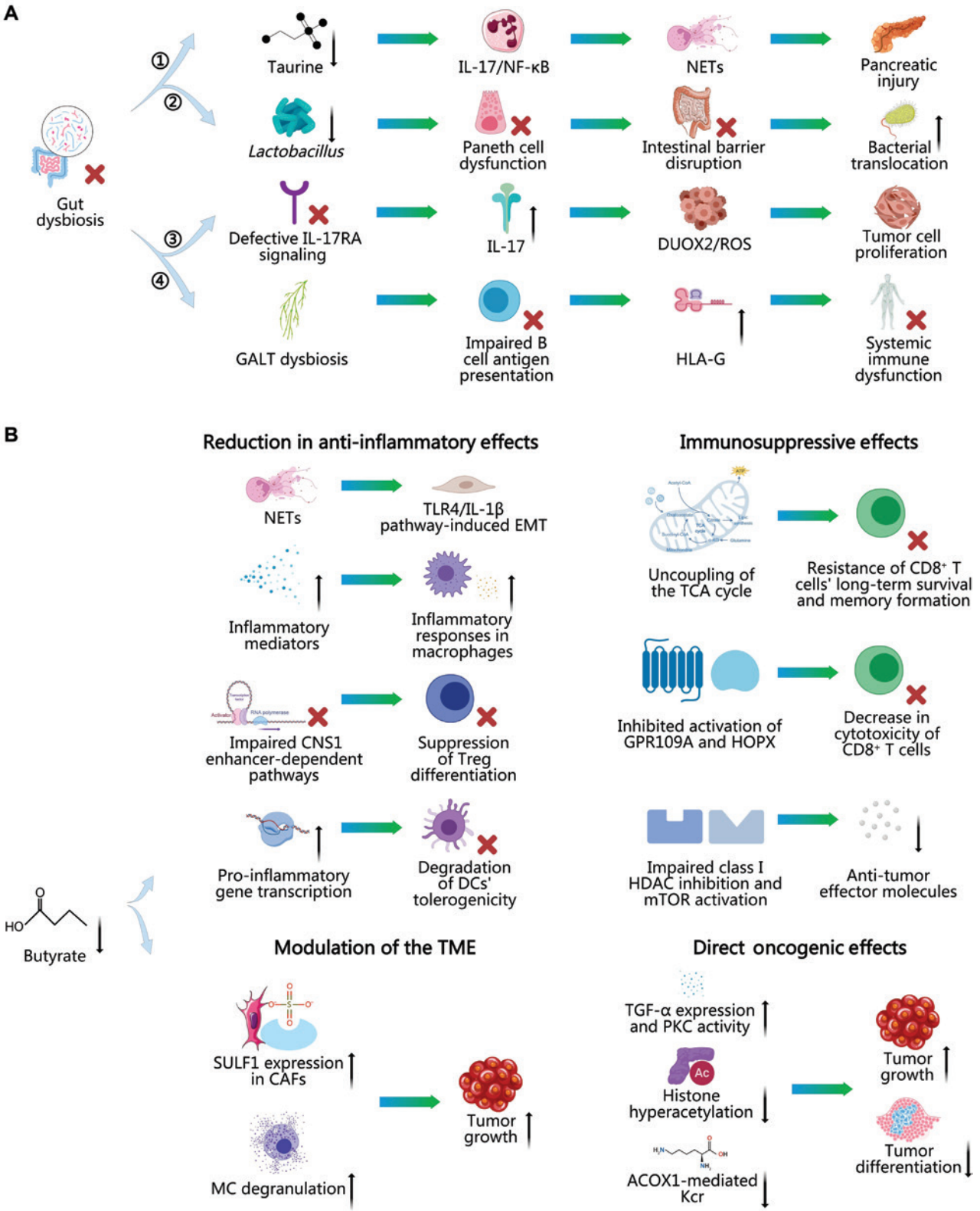


Figure 2 Gut dysbiosis and gut microbial metabolite butyrate reduction as potential drivers of pancreatic tumorigenesis. (A) Gut dysbiosis promotes pancreatic tumorigenesis through multiple pathways. ①: Gut dysbiosis, characterized by reduced *Bacteroides uniformis*, diminishes taurine production and increases colonic IL-17 release, which activates the IL-17/NF-κB signaling cascade in neutrophils, inducing NETs

formation and exacerbating pancreatic tissue injury. ②: Loss of *Lactobacillus* resulting from intestinal epithelial TLR4 deficiency disrupts Paneth cell function, leading to decreased secretion of antimicrobial peptides, such as lysozyme and α-defensins, compromised intestinal barrier integrity, and enhanced bacterial translocation to the pancreas. ③: Defective gut epithelial IL-17RA signaling promotes expansion of Th17 cells and IL-17F-producing B cells. Elevated systemic IL-17 activates the DUOX2 pathway in pancreatic tumor cells, generating excessive ROS that accelerate tumor cell proliferation. ④: GALT dysbiosis, characterized by *Klebsiella pneumoniae* enrichment, correlates with impaired B cell antigen presentation and upregulation of the immune checkpoint molecule, HLA-G, ultimately contributing to systemic immune dysfunction that underlies PDAC development. (B) Butyrate reduction drives pancreatic tumorigenesis through multifaceted mechanisms. (1) Reduction in anti-inflammatory effects: butyrate deficiency leads to increased NETs formation, which activates the TLR4/IL-1β/EMT axis; upregulation of inflammatory mediators, including NO, IL-6, and IL-12p40, in macrophages; suppression of Treg differentiation *via* impaired CNS1 enhancer-dependent pathways; and degradation of DC tolerogenicity due to increased pro-inflammatory gene transcription. These changes collectively result in sustained low-grade inflammation, promoting epithelial transformation. (2) Immunosuppressive effects: butyrate deficiency leads to the uncoupling of the TCA from glycolytic input in $CD8^+$ T cells, compromising the long-term survival and memory formation; inhibited activation of GPR109A and HOPX decreases $CD8^+$ T cell cytotoxicity, weakening anti-tumor immunity; impaired class I HDAC inhibition and mTOR activation reduces anti-tumor effector molecules, such as CD25, IFN-γ, and TNF-α. (3) Modulation of the TME: butyrate deficiency relieves inhibition of $SULF1^+$ CAFs and promotes MC degranulation, thereby amplifying the tumor-supportive functions and promoting tumor growth. (4) Direct oncogenic effects: butyrate deficiency relieves inhibition of TGF-α expression and PKC activity and suppresses histone hyperacetylation and ACOX1-mediated Kcr, which promotes tumor growth and impedes tumor differentiation. ACOX1, acyl-CoA oxidase 1; CAFs, cancer-associated fibroblasts; CD25, cluster of differentiation 25; CNS1, conserved non-coding sequence 1; DCs, dendritic cells; DUOX2, dual oxidase 2; EMT, epithelial-mesenchymal transition; GALT, gut-associated lymphoid tissue; GPR109A, G protein-coupled receptor 109A; HDAC, histone deacetylase; HLA-G, human leukocyte antigen-G; HOPX, homeodomain-only protein X; IFN-γ, interferon-gamma; IL-12p40, interleukin-12 subunit p40; IL-17, interleukin-17; IL-17RA, IL-17 receptor A; IL-1β, interleukin-1 beta; IL-6, interleukin-6; Kcr, lysine crotonylation; MC, mast cell; mTOR, mammalian target of rapamycin; NETs, neutrophil extracellular traps; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; PDAC, pancreatic ductal adenocarcinoma; PKC, protein kinase C; ROS, reactive oxygen species; SULF1, sulfatase 1; TCA, tricarboxylic acid; TGF-α, transforming growth factor-alpha; Th17, T helper 17; TLR4, Toll-like receptor 4; TME, tumor microenvironment; TNF-α, tumor necrosis factor-alpha; Treg, regulatory T cell. The scientific illustrations in this manuscript were created with MedPeer (medpeer.cn).

a role for $CX3CR1^+$ mononuclear phagocytes, which can engulf gut microbes without triggering inflammation and subsequently transport gut microbes to mesenteric lymph nodes, potentially allowing further migration to the pancreas *via* lymphatic drainage[169]. Together, these findings indicated that gut microorganisms may infiltrate pancreatic tissue through mucosal and immune cell-mediated routes, contributing to local immune modulation and TME remodeling.

Remote regulation of the pancreatic TME

In addition to direct migration, gut microbiota can promote PDAC progression through systemic, metabolite-mediated, and immunologic mechanisms. Transcriptomic profiling by Thomas et al. showed that the presence of gut microbiota in PDAC xenografts upregulated multiple oncogenes and survival-associated genes, indicating that microbial signals can reprogram tumor gene expression, even at a distance[141,170]. Similarly, Yu et al.[171] reported that gut microbiota suppressed intratumoral NK cell infiltration and activation. Because no microbes were detected within the tumors of the xenograft model, this effect was attributed to microbiota-derived metabolites. Gut dysbiosis in PDAC also perturbs bile acid metabolism, leading to elevated circulating bile acids that promote tumor progression by activating bile acid receptors in tumor cells[163]. Moreover, beneficial SCFA-producing bacteria, which enhance $CD8^+$ T cell activity and inhibit tumor growth, are markedly reduced in PDAC patients, resulting in impaired cytotoxic T cell responses and accelerated tumor progression[155,172]. In addition, lipopolysaccharide (LPS), a pro-inflammatory component of Gram-negative bacterial cell walls, can enhance PDAC cell invasiveness *via* activation of the TLR4/myeloid differentiation primary response 88 (MyD88) signaling pathway[173]. Together, these findings demonstrated that the gut microbiota can shape PDAC progression through two complementary mechanisms: direct translocation to the pancreas with integration into the TME; and remote regulation of pancreatic TME *via* transcriptomic, immunologic, and metabolic pathways. Through these interactions, microbial dysbiosis fosters an immunosuppressive and tumor-promoting environment. The dual mechanisms of microbial translocation and remote regulation in PDAC progression are summarized in **Figure 3**.

Gut and intratumoral microbiota regulate the TME

The gut microbiota exerts a profound influence on the TME of PDAC, modulating immune composition, cell polarization, and cytokine signaling to shape disease progression. Pushalkar et al.[162] demonstrated that the gut microbiota promotes pancreatic tumor progression by inducing peritumoral

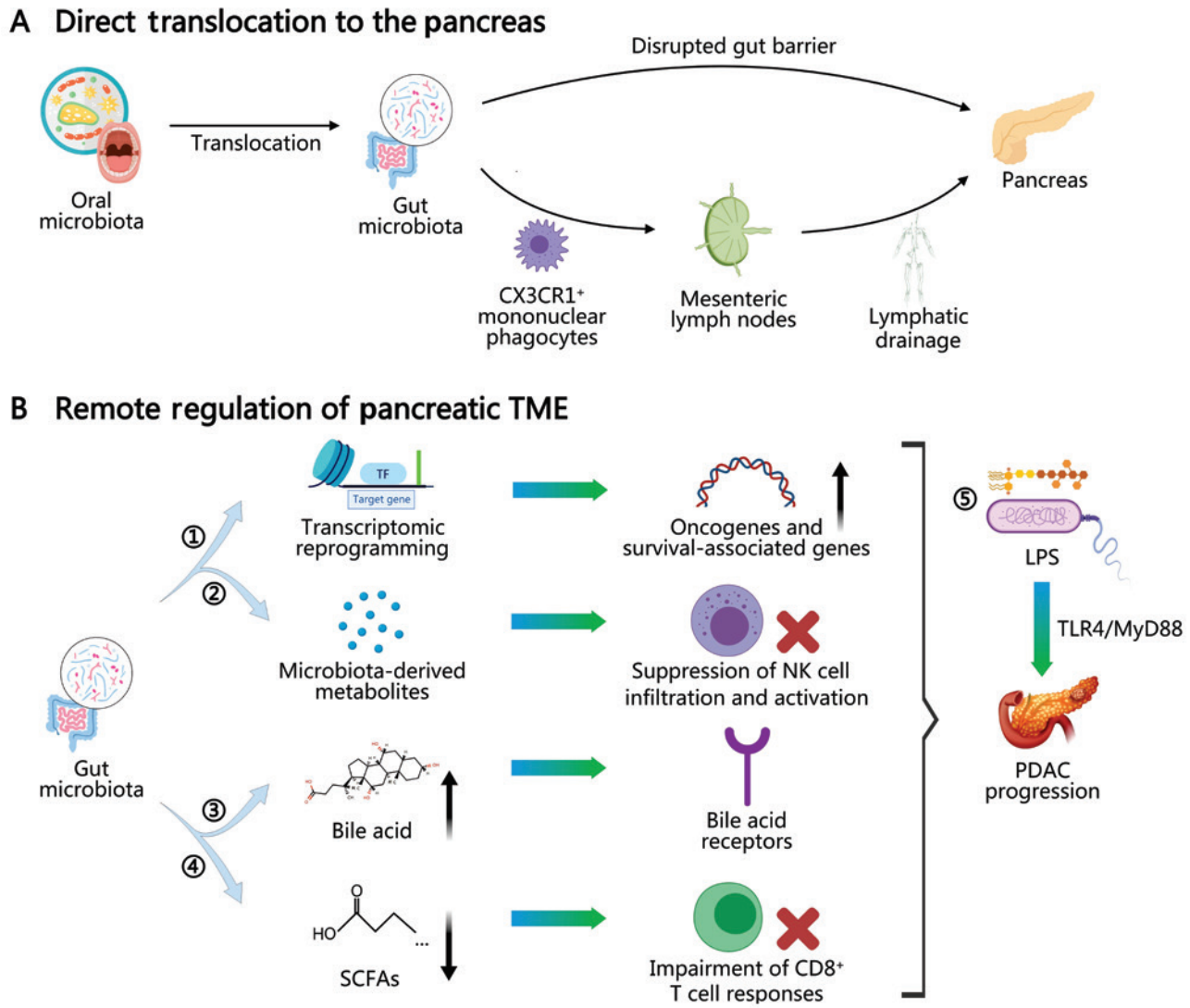


Figure 3 Dual mechanisms of microbial direct translocation and remote regulation in PDAC progression. (A) Direct translocation to the pancreas. Gut microbiota, potentially originating from the oral microbiome, can reach the pancreas through two principal routes: direct translocation across the disrupted gut barrier, or non-inflammatory uptake by CX3CR1$^+$ mononuclear phagocytes that engulf gut microbes and transport the gut microbes to mesenteric lymph nodes, enabling subsequent migration to the pancreas *via* lymphatic drainage. These findings reveal an "oral-gut-pancreas" microbial transmission axis and microorganisms that translocate to the pancreas participate in local immune modulation and TME remodeling, driving PDAC progression. (B) Remote regulation of pancreatic TME. ①: Microbial signals can remotely reprogram target gene expression *via* transcription factors, upregulating multiple oncogenes and survival-associated genes. ②: Microbiota-derived metabolites suppress intratumoral NK cell infiltration and activation. ③: Gut dysbiosis in PDAC perturbs bile acid metabolism, leading to elevated circulating bile acids that activate bile acid receptors on tumor cells. ④: Depletion of beneficial microbiota-produced SCFAs results in the impairment of CD8$^+$ T cell responses, weakening anti-tumor immunity. ⑤: LPS, a pro-inflammatory component of Gram-negative bacterial cell walls, enhances tumor cell invasiveness through the activation of the TLR4/MyD88 signaling pathway. The aforementioned mechanisms collectively promote PDAC progression. CX3CR1, C-X3-C motif chemokine receptor 1; LPS, lipopolysaccharide; MyD88, myeloid differentiation primary response 88; NK, natural killer; PDAC, pancreatic ductal adenocarcinoma; SCFAs, short-chain fatty acids; TLR4, Toll-like receptor 4; TME, tumor microenvironment. The scientific illustrations in this manuscript were created with MedPeer (medpeer.cn).

immunosuppression. Microbial ablation markedly increased cytotoxic function of CD8$^+$ T cells and antigen-presenting, pro-inflammatory M1-like TAMs in murine models, while microbial ablation reduced immunosuppressive MDSCs and M2-like TAMs. Mechanistically, the gut microbiota exerted these pro-tumor effects *via* activation of pattern recognition

receptors (PRRs), including TLR2 and TLR5. Yin et al.[174] further showed that the gut microbiota-derived metabolite, LPS, accelerates PDAC progression by upregulating PD-L1 expression through the TLR4/MyD88/protein kinase B (AKT)/NF-κB signaling cascade. This pathway promotes immune escape by driving T cell exhaustion and enhancing cancer cell resistance to cytotoxic lymphocytes. Similarly, Sethi et al.[175] reported that microbiota depletion in mouse models enhanced anti-tumor immunity by increasing Th1 ($IFN\gamma^+CD4^+CD3^+$) and Tc1 ($IFN\gamma^+CD8^+CD3^+$) cell populations and reducing pro-tumor IL-17a$^+$ ($IL17a^+CD3^+$) and IL-10$^+$ ($IL10^+CD4^+CD3^+$) immune subsets. Together, these findings indicated that the gut microbiota regulates the balance between pro- and anti-tumor immune responses within the TME. A Mendelian randomization analysis identified 20 gut microbial species that may modulate the progression of 4 pancreatic tumor subtypes through immune mediators, such as IL-6, CD4 expression on naïve $CD4^+$ T cells and SSC-A on HLA-DR^+ NK cells[13]. In addition, Vietsch et al.[142] analyzed immune and microbial profiles from the GALT of patients with PDAC and colonic disease. PDAC patients displayed reduced B cell function and diminished MHC class II surface receptor expression on B cells, suggesting dysbiosis-driven immune suppression. Collectively, these studies underscored the multifaceted role of the gut and intratumoral microbiota in orchestrating immune dynamics within the pancreatic TME. Through regulation of T cells, NK cells, TAMs, MDSCs, and B cells, gut microbiota shape the immunologic landscape toward a pro- or anti-tumor state, thereby profoundly influencing PDAC progression.

In addition to the gut microbiota, the intratumoral microbiota also have a pivotal role in shaping the pancreatic TME. Riquelme et al.[164] identified striking differences in intratumoral microbial composition between short-term survivors (STS) and long-term survivors (LTS) with PDAC. Tumors from LTS patients exhibited significantly higher microbial alpha-diversity with enrichment of *Pseudoxanthomonas*, *Streptomyces*, *Saccharopolyspora*, and *Clostridium*. Notably, the abundance of *Pseudoxanthomonas*, *Streptomyces*, and *Saccharopolyspora* are positively correlated with intratumoral $CD8^+$ T cell infiltration, suggesting that tumor microbiome diversity and these genera may foster antitumor immunity by enhancing $CD8^+$ T cell recruitment and activation. Similarly, Li et al.[176] reported that 16S rRNA levels in pancreatic tumors correlate positively with macrophage infiltration, the expression of CD86, and antigen-presenting molecules but inversely with CD206 expression and tumor weight. These findings indicated that intratumoral microbial abundance influences macrophage polarization and antigen-presenting capacity, thereby shaping immune dynamics within the TME.

Halimi et al.[165] cultured bacterial isolates from cystic pancreatic lesions associated with invasive cancer and identified 15 viable species. Among the species, *Enterobacter cloacae* HGD2 (H2), *Enterococcus faecium* H2, *Enterococcus faecalis* LGD2 (L2), and *Klebsiella pneumoniae* Cancer2 (C2) demonstrated robust survival in normal pancreatic and PDAC cell lines. In contrast, *Granulicatella adiacens* H1, *Enterococcus faecalis* C1, and *Klebsiella oxytoca* H1 caused extensive DNA damage and cell death in PDAC cells, whereas *Streptococcus anginosus* (H2/C2) and *Enterococcus faecium* H2 induced only mild cytotoxicity. These results suggest that some intratumoral bacterial species can directly contribute to PDAC progression by damaging pancreatic cells and altering genomic stability.

The relationship between intratumoral microbes and the immune system appears to be bidirectional. Li et al.[176] stratified PDAC tumors into "hot" ($CD8^+$ T cell-enriched) and "cold" ($CD8^+$ T cell-deficient) phenotypes. Distinct microbial profiles were observed. Specifically, hot tumors contain higher levels of *Arthrobacter* and *Bacillus* at the genus level and Methylobacteriaceae at the family level, whereas cold tumors were dominated by *Salirhabdus* and Oxalobacteraceae. Interestingly, hot tumors also displayed overall higher bacterial abundance, suggesting that tumor-associated T cells may influence microbial composition, thereby establishing a T cell-microbiota coupling within the TME.

Together, these studies revealed that gut and intratumoral microbiota actively remodel the pancreatic TME through multifaceted mechanisms. Gut and intratumoral microbiota modulate immune cell infiltration and polarization, including T cells, NK cells, TAMs, MDSCs, and B cells, while some bacterial species directly inflict DNA damage or cytotoxic stress on pancreatic cells. Moreover, immune components of the TME, particularly T cells, can reciprocally shape the intratumoral microbial landscape. This bidirectional interaction underscores a dynamic host-microbiota crosstalk that critically influences PDAC progression.

Intratumoral microbiota promotes resistance to therapy in PDAC

Chemotherapy remains the cornerstone of PDAC treatment. Combination regimens, such as FOLFIRINOX, and gemcitabine plus nab-paclitaxel (GnP) represent standard first-line therapies for patients with metastatic PDAC[177]. However, emerging evidence indicates that the intratumoral microbiota can mediate therapeutic resistance through metabolic, genetic, and redox-regulatory mechanisms.

A landmark study revealed that some bacterial species within PDAC tumors express cytidine deaminase (CDD), an enzyme that metabolizes gemcitabine into the inactive form, 2′,2′-difluorodeoxyuridine. Notably, the long isoform (CDD_L) of this enzyme was identified as the key mediator of this process, providing a direct microbial mechanism for chemoresistance[166,178]. These findings highlighted the potential for tumor-resident bacteria to inactivate chemotherapeutic agents within the TME, diminishing treatment efficacy. In addition to drug metabolism, the intratumoral microbiota can modulate redox homeostasis, thereby protecting tumor cells from chemotherapy-induced

oxidative damage. Obese mice bearing PDAC exhibited enrichment of microbial cells producing queuosine, a metabolite that enhances tumor resilience against oxidative stress by upregulating peroxiredoxin 1 (PRDX1), conferring resistance to both gemcitabine and nab-paclitaxel[179]. Similarly, alterations in the microbial metabolome lead to enrichment of "protective" metabolites in type 2 diabetic mice (menaquinol and queuine) that act as antioxidants, reducing chemotherapy-induced ROS accumulation and promoting drug resistance[180]. In other cancer types, the intratumoral microbiome has been shown to influence responsiveness to immune checkpoint blockade, including anti-PD-L1 and anti-CTLA-4 therapies[181-183]. Although this mechanism has not been definitively established in PDAC, there is a possibility that similar microbial-mediated immune modulation could underlie resistance to emerging immunotherapeutic strategies in PDAC.

Together, these findings demonstrated that the intratumoral microbiota contributes to PDAC therapy resistance through multiple pathways, as follows: enzymatic drug inactivation; metabolic protection from oxidative stress; and potentially modulation of immune checkpoint responsiveness. Understanding these microbial-drug interactions may pave the way for microbiota-targeted interventions to enhance treatment efficacy in PDAC.

Clinical applications and translational prospects

Building upon the preceding evidence of gut microbiota dysregulation in PDAC and the roles in tumorigenesis, progression, and metastasis, this section explores the emerging clinical implications and translational potential of these findings. Specifically, there is a focus on how gut microbiota signatures may contribute to early diagnosis, prognostic assessment, and therapeutic optimization in PDAC. By integrating mechanistic insights with clinical observations, these perspectives aim to bridge fundamental microbiome research with precision oncology, thereby guiding future strategies for clinical translation and individualized patient management.

Potential diagnostic and prognostic biomarkers from the gut microbiota

Although numerous microbial taxa differ in abundance between patients with PDAC and healthy individuals, only a subset exhibits consistent and reproducible potential as diagnostic or prognostic biomarkers.

Diagnostic biomarkers

A large multinational metagenomic study encompassing Japanese, Spanish, and German cohorts identified consistent alterations in gut microbial composition at multiple levels. At the species level, *Veillonella atypica*, *Veillonella parvula*, *Streptococcus anginosus*, and *Streptococcus oralis* were shown to be consistently enriched in PDAC, whereas *Faecalibacterium prausnitzii* was significantly depleted [false discovery rate (FDR) < 0.1]. Functionally, pathways related to terpenoid backbone biosynthesis, ATP-binding cassette (ABC) transporters, pyruvate metabolism, mevalonate pathway, and osmoprotectant transport systems were enriched, while amino acid and secondary metabolite biosynthesis, histidine metabolism, and dissimilatory sulfate reduction were depleted (FDR < 0.1). Collectively, these consistent microbial and functional alterations highlight potential biomarkers for PDAC detection[115].

Other studies have validated the diagnostic value of microbiome signatures using machine learning-based classifiers. A least absolute shrinkage and selection operator (LASSO) logistic regression model integrating several fecal species distinguished PDAC patients from controls in a Spanish cohort with an area under the receiver operating characteristic curve (AUROC) of 0.84. The top positively weighted species were *Methanobrevibacter smithii*, *Alloscardovia omnicolens*, *Veillonella atypica*, and *Bacteroides finegoldii*[118].

Serum CA19-9, a conventional biomarker for PDAC, offers only moderate diagnostic accuracy (sensitivity, 0.80; specificity, 0.75)[184]. Diagnostic performance markedly improved when combined with the microbiota-based models; specifically, CA19-9 plus the aforementioned model improved the AUROC from 0.84 to 0.94[118]. Chen et al.[117] developed more refined models in another study based on a Chinese cohort using LASSO and random forest algorithms. Model 1, based on 9 genera (e.g., *Sporotomaculum*, *Blautia*, *Larssonia*, *Clostridioides*, and *Anaerobutyricum*), achieved an AUROC of 0.923. Model 2, based on eight species, including *Blautia hominis*, *Desulfovibrio* spp., and *Modestobacter apidist*, reached an AUROC of 0.853. Combined with CA19-9, the predictive accuracy increased to an AUROC of 0.977 and 0.953, respectively, outperforming CA19-9 alone (0.825). The best performance occurred in older patients [≥55 years of age (AUROC = 0.993)].

In addition, specific taxa may serve as individual diagnostic markers. Elevated *Streptococcus* abundance has been associated with increased PDAC risk in a Chinese cohort, while mouse models have suggested that upregulated microbial polyamine biosynthesis pathways are implicated in early tumorigenesis and diagnostic prediction[110,137].

Prognostic biomarkers

There are also some gut microbes that may serve as potential biomarkers for PDAC prognosis. The aforementioned multinational study showed that unknown *Alistipes*, *Faecalibacterium prausnitzii*, and Enterobacteriaceae species were linked to a favorable prognosis, whereas *Ruminococcus torques* predicted poorer outcomes. Higher abundances of *Eubacterium* spp. CAG:38, *Phascolarctobacterium* spp., *Clostridium* spp. AT4, Enterobacteriaceae spp., unknown Clostridiales, *Faecalibacterium prausnitzii*, and *Oscillibacter*

spp. 57-20 were negatively correlated with progressive disease, while *Bacteroides coprocola*, *Alistipes onderdonkii*, and unknown Clostridiales were positively correlated with progression[115]. Furthermore, in an exploratory Chinese cohort study, elevated fecal *Lactobacillus* abundance has been linked to improved progression-free survival (PFS) and overall survival (OS) in PDAC patients with *Lactobacillus reuteri* exerting direct antitumor effects[128]. Similarly, a Japanese cohort study has confirmed that higher *Bifidobacterium* levels are associated with better responses to neoadjuvant chemotherapy[185].

Microbiome-based machine learning models have also identified microbial taxa predictive of metastatic potential in a single-center Italian cohort study. Species such as *Anaerostipes hadrus*, *Coprobacter secundus*, *Clostridium* spp. 619, and *Roseburia inulinivorans* (species level), *Porphyromonas* and *Odoribacter* (genus level), and Rhodospirillaceae, Clostridiaceae, and Peptococcaceae (family level) demonstrated the strongest discriminatory power to distinguish between metastatic and non-metastatic PDAC. Functionally, non-metastatic PDAC was characterized by upregulated biosynthesis and metabolism of amino acids, increased transcriptional function, and enriched polar metabolites, whereas metastatic PDAC exhibited enhanced signal transduction and elevated glutamic acid and metastasis-associated diacylglycerols. Importantly, non-metastatic PDAC uniquely enriched oxidized fatty acids, including linoleic acid, linolenic acid, and eicosapentaenoic acid (EPA)[12]. Moreover, *Streptococcus* abundance also exhibited predictive potential for early hepatic metastasis (AUROC = 0.796)[110].

Together, these findings suggested that gut microbial signatures, alone or in combination with established biomarkers (e.g., CA19-9), hold strong promise for early diagnosis, prognostic assessment, and metastasis prediction in PDAC. The integration of metagenomic, metabolomic, and clinical data may further enhance predictive accuracy and pave the way toward microbiota-based precision diagnostics in PDAC.

Potential therapeutic strategies targeting the gut microbiota

Given the established prevalence of gut dysbiosis in PDAC and the mechanistic role in tumor initiation and progression, targeting the gut microbiota and gut microbiota metabolites represent a promising therapeutic approach. Moreover, integrating microbiota-targeted interventions with conventional treatments, such as chemotherapy or immunotherapy, may yield synergistic benefits that surpass the efficacy of either approach alone.

Probiotic-based interventions

Probiotic supplementation has emerged as a viable strategy for restoring microbial balance and modulating the TME. Multiple studies have demonstrated that probiotics delay cancer progression by reshaping the gut and intratumoral microbiota with documented efficacy in colorectal, hepatic, and pancreatic malignancies[186-188]. Combination probiotic formulations have shown notable therapeutic potential in mouse models of PDAC, including reduced tumor cell pleomorphism, induced tumor cell DNA damage and apoptosis, decreased cancer-associated stromatogenesis, alleviation of chemotherapy-induced intestinal toxicity and dysbiosis, preservation of hematologic function, and modulation of host metabolism[189,190]. In addition, the AJ2 probiotic combination in PDAC mice notably enhanced NK cell cytotoxicity and IFN-γ secretion, thereby promoting differentiation of poorly differentiated tumors and inhibiting their growth and metastasis[191]. In addition to mouse models, probiotics have also demonstrated therapeutic efficacy against PDAC in clinical studies. In a randomized controlled trial, probiotics exhibited increased tumor-infiltrating $CD8^+$ T cells and IFN-γ expression, attenuated systemic levels of pro-inflammatory cytokines, such as IL-1β, IL-6, and IL-10, reduced postoperative infectious complications, including bacteremia, and alleviated non-infectious complications, such as anastomotic leakage, diarrhea, and abdominal distension[192].

Therapeutic role of Lactobacillus spp.

Among probiotics, *Lactobacillus* exhibits the strongest evidence for antitumor efficacy in PDAC. Clinical data indicated that co-administration of *Lactobacillus casei* and *Lactobacillus rhamnosus* significantly prolong PFS and OS compared to controls[188]. Similarly, in mouse models, combined treatment with *Lactobacillus paracasei* GMNL-133 and *Lactobacillus reuteri* GMNL-89 suppressed tumor progression, reduced vimentin and Ki-67 expression, and improved the efficacy and tolerability of gemcitabine chemotherapy[193].

Mechanistically, *Lactobacillus* secretes ferrichrome, a siderophore metabolite that drives macrophage polarization toward the M1 phenotype *via* the TLR4-ferroportin signaling axis[194,195]. This polarization suppresses the pro-invasive behavior of TAMs, enhances $CD8^+$ T cell infiltration, and potentiates anti-PD-L1 immunotherapy[194]. Ferrichrome also induces p53-dependent apoptosis in PDAC cells and shows activity against 5-FU-resistant PDAC, without significant toxicity in preclinical models[196]. Furthermore, enrichment of *Lactobacillus*, particularly *Lactobacillus reuteri*, has been associated with improved PDAC outcomes through enhanced NK cell infiltration into the TME, potentially representing a microbiota-mediated immune activation mechanism[128]. An engineered *Lactobacillus rhamnosus* GG strain coated with a gallium-polyphenol network applied in murine models further exemplifies translational innovation in microbiota therapeutics. This system selectively targets tumor-promoting Proteobacteria and LPS, disrupting bacterial iron respiration and thereby attenuating TLR signaling. The downstream effects include reduced PD-L1 and IL-1β expression, diminished immunosuppressive myeloid populations, enhanced cytotoxic T lymphocyte infiltration, and improved efficacy of gemcitabine and α-PD-L1 therapy[197].

Therapeutic potential of Clostridium butyricum

Clostridium butyricum also exhibits antitumor activity in mouse models of PDAC, primarily mediated by the metabolite, butyrate. Butyrate inhibits tumor progression by downregulating superoxide dismutase 2 (SOD2) to induce superoxide stress, enhancing free fatty acid uptake while impairing lipolysis to promote intracellular lipid accumulation, and sensitizing PDAC cells to ferroptosis inducers, such as RAS-selective lethal 3 (RSL3)[198]. Conjugation of *Clostridium butyricum* with a matrix metalloproteinase-2 (MMP-2)-responsive liposomal nanosystem has demonstrated dual effects: extracellular matrix (ECM) remodeling through vactosertib delivery to silence pancreatic stellate cells (PSCs); and improved gemcitabine efficacy *via* competitive inhibition of tumor-colonizing γ-proteobacteria. This approach enhanced gemcitabine-induced immunogenic cell death, promoted effector immune infiltration, and exemplified a combinatorial microbiota-nanomedicine therapeutic strategy[199]. However, the application of *Clostridium butyricum* or butyrate remains in the preclinical stage.

Synbiotic therapy

Synbiotics (combinations of probiotics and prebiotics) offer additional benefits by supporting the selective growth of beneficial microbes[200]. In a randomized controlled trial of patients undergoing pancreatoduodenectomy, synbiotic supplementation containing four different lactic acid bacteria (*Pediococcus pentosaceus* 5-33:3, *Leuconostoc mesenteroides* 77:1, *Lactobacillus paracasei* subspecies *paracasei* F19, and *Lactobacillus plantarum* 2362) and four bioactive fibers (beta-glucan, inulin, pectin, and resistant starch) significantly reduced postoperative infection rates[201]. Another clinical study demonstrated that synbiotics (containing probiotics and inulin) induced greater $CD8^+$ T cell infiltration, elevated IFN-γ expression, and reduced inflammatory cytokines compared to the same probiotics alone. Synbiotics also reduced the incidence of postoperative complications, including bacteremia, pneumonia, and diarrhea, suggesting superior efficacy relative to single-strain probiotics[192].

Fecal microbiota transplantation (FMT)

FMT has shown therapeutic promise beyond gastrointestinal diseases, such as *Clostridium difficile* infection, irritable bowel syndrome (IBS), and IBD, extending to cancers, including colorectal carcinoma, melanoma, and PDAC[164,202-204]. FMT from LTS reprogrammed the intratumoral microbiota, enhanced $CD8^+$ T cell infiltration and activation, and inhibited tumor growth in mouse models of PDAC, whereas FMT from advanced patients promoted tumor progression and increased immunosuppressive populations. These findings suggested that the therapeutic efficacy of FMT is largely mediated by beneficial bacterial taxa (e.g., *Lactobacillus*) and metabolites, such as indole-3-acetic acid (3-IAA)[128,205]. Currently, several clinical trials investigating FMT for PDAC treatment are ongoing.

Microbial metabolite supplementation

Supplementation with microbiota-derived metabolites represents another promising strategy. Butyrate prevents tumorigenesis and enhances the efficacy of gemcitabine while mitigating the side effects[126,206]. Similarly, 3-IAA enhances the chemotherapy response by being oxidized by neutrophil myeloperoxidase to generate ROS, leading to autophagy inhibition and suppressed cancer cell proliferation[205]. TMAO, either directly supplemented or generated from dietary choline, can reprogram TAMs toward an immunostimulatory phenotype, activate type I interferon signaling, and improve response to immune checkpoint blockade[207]. Nevertheless, all these findings have only been validated in mouse models and clinical trials are required to confirm translational potential.

Dietary modulation of the gut microbiota

Beyond direct interventions targeting the gut microbiota and gut microbiota metabolites, emerging evidence suggests that supplementation with specific bioactive compounds and adoption of particular dietary regimens may also exert therapeutic effects in PDAC by reshaping the gut microbiota. Resveratrol, a natural polyphenol, has been shown to potentiate α-PD-1 immunotherapy efficacy in PDAC by modulating the gut microbiota to enhance arachidonic acid metabolism and increase prostaglandin D_2 (PGD_2) levels. Elevated PGD_2 subsequently activates the prostaglandin D receptor 1 (DP1), promoting $CD8^+$ T cell infiltration into tumors and strengthening antitumor immunity[129]. A Japanese single-center, randomized, controlled pilot trial demonstrated that supplementation with 1-kestose, a fructo-oligosaccharide, alongside chemotherapy improved PDAC patient outcomes by modulating the gut microbiota. This intervention reduced *Escherichia coli* abundance, serum CA19-9 levels, and the neutrophil-to-lymphocyte ratio (NLR), thereby mitigating systemic inflammation[208].

Dietary regimens may also influence therapeutic efficacy through microbiota-mediated mechanisms. The ketogenic diet, characterized by low carbohydrate and high fat intake, has been reported to enhance gemcitabine efficacy in PDAC, potentially by altering microbial composition[209]. Similarly, a purified soy-free diet may improve phosphatidylinositol 3-kinase (PI3K) inhibitor efficacy by preventing the gut microbiota-dependent production of soyasapogenols, which induce hepatic cytochrome P450, family 3, subfamily a, polypeptide 11 (CYP3A11) and accelerate drug clearance, thereby diminishing antitumor activity[210]. In addition, a fasting-mimicking diet (FMD), characterized by cyclic low-calorie restriction, may suppress PDAC progression by enriching butyrate-producing gut bacteria, elevating pancreatic butyrate levels, and promoting Kcr, ultimately inhibiting tumor cell proliferation[126]. While several clinical trials exploring dietary interventions for PDAC have been conducted, more diverse and large-scale clinical studies are needed to validate their efficacy.

Antibiotic-based modulation: potential and caution

Given the prevalence of gut dysbiosis in PDAC, antibiotic-based depletion of the gut microbiota has been explored as a potential therapeutic approach. Preclinical studies suggest that antibiotics may suppress tumor-promoting metabolic and inflammatory pathways, enhance apoptosis-related processes, and modulate NK and T cell activity within the TME, thereby improving responses to chemotherapy and targeted therapy[171,175,210,211]. However, these effects have been demonstrated only in murine models and extrapolating to humans is challenging. The gut microbiota in humans has a far more complex immunometabolic role, the indiscriminate depletion of which may yield counterproductive or deleterious effects. Evidence indicates that antibiotic-induced microbiota depletion can impair antitumor immunity by eliminating beneficial bacteria, such as *Lactobacillus* and reducing IL-33 expression, which in turn suppresses the migration of group 2 innate lymphoid cells (ILC2s) from the gut to tumors and diminishes intratumoral tertiary lymphoid structures (TLSs)[128,212]. In summary, while preclinical data suggest potential benefits, the clinical translation of broad-spectrum antibiotics for PDAC treatment demands careful consideration. Given the complex immunomodulatory roles of the gut microbiota in humans, non-selective depletion risks disrupting protective microbial communities and compromising antitumor immunity. Current evidence, which is largely derived from murine models, is insufficient to support routine clinical application. Therefore, future research must prioritize the development of targeted strategies that precisely inhibit tumor-promoting microbial populations and robust clinical evidence is needed to define safe and effective therapeutic windows.

Challenges and future perspectives

In this review we systematically examined the growing body of evidence linking the gut microbiota to PDAC, emphasizing the multifaceted interactions among microbial communities, tumorigenesis, and host systems. Moving forward, research must transcend descriptive profiling of microbial alterations and focus on delineating the mechanistic pathways through which the gut microbiota modulates pancreatic tumorigenesis and progression. Gut dysbiosis may act as a driver in early tumorigenesis by disrupting immune and metabolic homeostasis with reduced butyrate production promoting inflammation, impairing immune surveillance, and altering gene expression. Gut and intratumoral microbiota influence disease evolution through bacterial translocation, remote immunometabolic regulation, and remodeling of the TME during PDAC progression. These insights also underscore the translational potential of gut microbiota in early detection, personalized therapy optimization, and prognostic stratification. Collectively, emerging strategies, including FMT, probiotic and synbiotic supplementation, dietary modulation, and microbiota-sensitive antibiotic regimens, highlight the promise of tailored microbial modulation as a novel approach to PDAC management[213].

Despite these advances, several major challenges remain. Most existing studies have focused on associations rather than causality, leaving the direct mechanistic links between gut dysbiosis and pancreatic tumorigenesis largely unresolved. The gut microbiota functions as an ecologic network, in which perturbations to one taxon can reverberate throughout the system. Moreover, specific bacterial species may play context-dependent roles, acting as tumor-promoting or -suppressive agents depending on host and environmental factors[214]. Translational limitations are further compounded by interspecies discrepancies between human and murine microbiota. Some interventions, such as FMT, remain controversial. Recent evidence has suggested that "microbial mismatch" following transplantation may disrupt host metabolic and immune equilibrium, thereby attenuating therapeutic efficacy[215]. In addition, the paucity of large-scale, multicenter, prospective trials and the methodologic biases inherent in high-throughput sequencing and bioinformatics pipelines hinder the reproducibility and clinical validation of microbiota-targeted interventions.

Future progress will depend on integrative multi-omics strategies, combining metagenomics, transcriptomics, metabolomics, and single-cell genomics, to comprehensively map the gut microbiota-PDAC interaction network[216]. These approaches should be coupled with functional validation in physiologically relevant models and prospective clinical trials. The emergence of precision microbial engineering techniques, including synthetic biology-based tools and *in situ* genome editing of microbial communities, offers exciting prospects for targeted modulation of tumor-associated microbiota[217,218].

In summary, while the current understanding of the gut-pancreas axis remains incomplete, it holds transformative potential for the prevention, diagnosis, and treatment of PDAC. Realizing this promise will require sustained interdisciplinary collaboration across microbiology, oncology, bioinformatics, and artificial intelligence to translate microbiome science into clinically actionable strategies that enable precision diagnosis and personalized therapy.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

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References

1. Yang J, Xu R, Wang C, Qiu J, Ren B, You L. Early screening and diagnosis strategies of pancreatic cancer: a comprehensive review. Cancer Commun (Lond). 2021; 41: 1257-74.
2. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024; 74: 12-49.
3. Chen Q, Yin H, Jiang Z, He T, Xie Y, Mao W, et al. Poor clinical outcomes and immunoevasive contexture in CD161$^+$CD8$^+$ T cells barren human pancreatic cancer. J Immunother Cancer. 2024; 12: e008694.
4. Yin H, Chen Q, Gao S, Shoucair S, Xie Y, Habib JR, et al. The crosstalk with CXCL10-rich tumor-associated mast cells fuels pancreatic cancer progression and immune escape. Adv Sci (Weinh). 2025; 12: e2417724.
5. Wong CC, Yu J. Gut microbiota in colorectal cancer development and therapy. Nat Rev Clin Oncol. 2023; 20: 429-52.
6. Zhang X, Coker OO, Chu ES, Fu K, Lau HCH, Wang YX, et al. Dietary cholesterol drives fatty liver-associated liver cancer by modulating gut microbiota and metabolites. Gut. 2021; 70: 761-74.
7. Song Y, Lau HC, Zhang X, Yu J. Bile acids, gut microbiota, and therapeutic insights in hepatocellular carcinoma. Cancer Biol Med. 2023; 21: 144-62.
8. Yu X, Ou J, Wang L, Li Z, Ren Y, Xie L, et al. Gut microbiota modulate CD8$^+$ T cell immunity in gastric cancer through Butyrate/GPR109A/HOPX. Gut Microbes. 2024; 16: 2307542.
9. Riquelme E, Maitra A, McAllister F. Immunotherapy for pancreatic cancer: more than just a gut feeling. Cancer Discov. 2018; 8: 386-8.
10. Hong J, Fu Y, Chen X, Zhang Y, Li X, Li T, et al. Gut microbiome changes associated with chronic pancreatitis and pancreatic cancer: a systematic review and meta-analysis. Int J Surg. 2024; 110: 5781-94.
11. Kaune T, Griesmann H, Theuerkorn K, Hämmerle M, Laumen H, Krug S, et al. Gender-specific changes of the gut microbiome correlate with tumor development in murine models of pancreatic cancer. iScience. 2023; 26: 106841.
12. Villani A, Fontana A, Panebianco C, Ferro C, Copetti M, Pavlovic R, et al. A powerful machine learning approach to identify interactions of differentially abundant gut microbial subsets in patients with metastatic and non-metastatic pancreatic cancer. Gut Microbes. 2024; 16: 2375483.
13. Chen Z, Wang Z, Bao H, Ma S. Gut microbiota and pancreatic cancer risk, and the mediating role of immune cells and inflammatory cytokines: a Mendelian randomization study. Front Immunol. 2024; 15: 1408770.
14. Khalaf N, El-Serag H, Kanwal F, Chan J. The influence of gut and tumor microbiome on pancreatic cancer outcomes. Gastroenterology. 2020; 159: 1184-5.
15. Stoop TF, Javed AA, Oba A, Koerkamp BG, Seufferlein T, Wilmink JW, et al. Pancreatic cancer. Lancet. 2025; 405: 1182-202.
16. Han J, Yin H, He T, He J, Jiang Z, Chen Q, et al. The evolutionary trajectory and prognostic value of GITR+ Tregs reprogramed by tumor-intrinsic PD-1/c-MET signaling in pancreatic cancer. Adv Sci (Weinh). 2025; 12: e00806.
17. Pu N, Chen Q, Han J, Xu Z, Jiang Z, He T, et al. Intratumoral IL-33$^+$CD4$^+$FoxP3$^+$ regulatory T cell infiltration determines poor clinical outcomes and intensive immunoevasive contexture in patients with pancreatic cancer after surgical resection: a cohort study. Int J Surg. 2025; 111: 6245-59.
18. Basturk O, Hong SM, Wood LD, Adsay NV, Albores-Saavedra J, Biankin AV, et al. A revised classification system and recommendations from the Baltimore Consensus Meeting for neoplastic precursor lesions in the pancreas. Am J Surg Pathol. 2015; 39: 1730-41.
19. Felsenstein M, Noë M, Masica DL, Hosoda W, Chianchiano P, Fischer CG, et al. IPMNs with co-occurring invasive cancers: neighbours but not always relatives. Gut. 2018; 67: 1652-62.
20. Cancer Genome Atlas Research Network. Integrated genomic characterization of pancreatic ductal adenocarcinoma. Cancer Cell. 2017; 32: 185-203.e13.
21. Kanda M, Matthaei H, Wu J, Hong SM, Yu J, Borges M, et al. Presence of somatic mutations in most early-stage pancreatic intraepithelial neoplasia. Gastroenterology. 2012; 142: 730-3.e9.
22. Jones S, Zhang X, Parsons DW, Lin JC, Leary RJ, Angenendt P, et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. Science. 2008; 321: 1801-6.
23. Waddell N, Pajic M, Patch AM, Chang DK, Kassahn KS, Bailey P, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature. 2015; 518: 495-501.
24. Bailey P, Chang DK, Nones K, Johns AL, Patch AM, Gingras MC, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. Nature. 2016; 531: 47-52.

25. Hingorani SR, Wang L, Multani AS, Combs C, Deramaudt TB, Hruban RH, et al. Trp53R172H and KrasG12D cooperate to promote chromosomal instability and widely metastatic pancreatic ductal adenocarcinoma in mice. Cancer Cell. 2005; 7: 469-83.
26. Morris JP 4th, Yashinskie JJ, Koche R, Chandwani R, Tian S, Chen CC, et al. α-Ketoglutarate links p53 to cell fate during tumour suppression. Nature. 2019; 573: 595-9.
27. Rajeshkumar NV, Dutta P, Yabuuchi S, de Wilde RF, Martinez GV, Le A, et al. Therapeutic targeting of the Warburg effect in pancreatic cancer relies on an absence of p53 function. Cancer Res. 2015; 75: 3355-64.
28. Blackford A, Serrano OK, Wolfgang CL, Parmigiani G, Jones S, Zhang X, et al. SMAD4 gene mutations are associated with poor prognosis in pancreatic cancer. Clin Cancer Res. 2009; 15: 4674-9.
29. Barriga FM, Tsanov KM, Ho YJ, Sohail N, Zhang A, Baslan T, et al. MACHETE identifies interferon-encompassing chromosome 9p21.3 deletions as mediators of immune evasion and metastasis. Nat Cancer. 2022; 3: 1367-85.
30. Szczepanski JM, Rudolf MA, Shi J. Clinical evaluation of the pancreatic cancer microenvironment: opportunities and challenges. Cancers (Basel). 2024; 16: 794.
31. Falcomatà C, Bärthel S, Schneider G, Rad R, Schmidt-Supprian M, Saur D. Context-specific determinants of the immunosuppressive tumor microenvironment in pancreatic cancer. Cancer Discov. 2023; 13: 278-97.
32. Vitorakis N, Gargalionis AN, Papavassiliou KA, Adamopoulos C, Papavassiliou AG. Precision targeting strategies in pancreatic cancer: the role of tumor microenvironment. Cancers (Basel). 2024; 16: 2876.
33. Opitz FV, Haeberle L, Daum A, Esposito I. Tumor microenvironment in pancreatic intraepithelial neoplasia. Cancers (Basel). 2021; 13: 6188.
34. Chen Q, Yin H, He J, Xie Y, Wang W, Xu H, et al. Tumor microenvironment responsive $CD8^+$ T cells and myeloid-derived suppressor cells to trigger CD73 inhibitor AB680-based synergistic therapy for pancreatic cancer. Adv Sci (Weinh). 2023; 10: e2302498.
35. Walter FM, Mills K, Mendonça SC, Abel GA, Basu B, Carroll N, et al. Symptoms and patient factors associated with diagnostic intervals for pancreatic cancer (SYMPTOM pancreatic study): a prospective cohort study. Lancet Gastroenterol Hepatol. 2016; 1: 298-306.
36. Goggins M, Overbeek KA, Brand R, Syngal S, Del Chiaro M, Bartsch DK, et al. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium. Gut. 2020; 69: 7-17.
37. Singh S, Tang SJ, Sreenarasimhaiah J, Lara LF, Siddiqui A. The clinical utility and limitations of serum carbohydrate antigen (CA19-9) as a diagnostic tool for pancreatic cancer and cholangiocarcinoma. Dig Dis Sci. 2011; 56: 2491-6.
38. Fahrmann JF, Schmidt CM, Mao X, Irajizad E, Loftus M, Zhang J, et al. Lead-time trajectory of CA19-9 as an anchor marker for pancreatic cancer early detection. Gastroenterology. 2021; 160: 1373-83.e6.
39. Pang TCY, Po JW, Becker TM, Goldstein D, Pirola RC, Wilson JS, et al. Circulating tumour cells in pancreatic cancer: a systematic review and meta-analysis of clinicopathological implications. Pancreatology. 2021; 21: 103-14.
40. Guven DC, Sahin TK, Yildirim HC, Aktepe OH, Dizdar O, Yalcin S. A systematic review and meta-analysis of the association between circulating tumor DNA (ctDNA) and prognosis in pancreatic cancer. Crit Rev Oncol Hematol. 2021; 168: 103528.
41. Lai X, Wang M, McElyea SD, Sherman S, House M, Korc M. A microRNA signature in circulating exosomes is superior to exosomal glypican-1 levels for diagnosing pancreatic cancer. Cancer Lett. 2017; 393: 86-93.
42. Bunduc S, Gede N, Váncsa S, Lillik V, Kiss S, Juhász MF, et al. Exosomes as prognostic biomarkers in pancreatic ductal adenocarcinoma-a systematic review and meta-analysis. Transl Res. 2022; 244: 126-36.
43. Li Y, Fan Z, Meng Y, Liu S, Zhan H. Blood-based DNA methylation signatures in cancer: a systematic review. Biochim Biophys Acta Mol Basis Dis. 2023; 1869: 166583.
44. Yin L, Pu N, Thompson E, Miao Y, Wolfgang C, Yu J. Improved assessment of response status in patients with pancreatic cancer treated with neoadjuvant therapy using somatic mutations and liquid biopsy analysis. Clin Cancer Res. 2021; 27: 740-8.
45. Zhang Y, Huang J, Chen M, Jiao LR. Preoperative vascular evaluation with computed tomography and magnetic resonance imaging for pancreatic cancer: a meta-analysis. Pancreatology. 2012; 12: 227-33.
46. Dalah E, Erickson B, Oshima K, Schott D, Hall WA, Paulson E, et al. Correlation of ADC with pathological treatment response for radiation therapy of pancreatic cancer. Transl Oncol. 2018; 11: 391-8.
47. Kleeff J, Korc M, Apte M, La Vecchia C, Johnson CD, Biankin AV, et al. Pancreatic cancer. Nat Rev Dis Primers. 2016; 2: 16022.
48. Cameron JL, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduodenectomies. Ann Surg. 2006; 244: 10-5.
49. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011; 364: 1817-25.
50. Groot VP, Rezaee N, Wu W, Cameron JL, Fishman EK, Hruban RH, et al. Patterns, timing, and predictors of recurrence following pancreatectomy for pancreatic ductal adenocarcinoma. Ann Surg. 2018; 267: 936-45.
51. Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul JL, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med. 2018; 379: 2395-406.
52. Khan N, Raza U, Ali Zaidi SA, Nuer M, Abudurousuli K, Paerhati Y, et al. Drugging the 'undruggable' KRAS: breakthroughs, challenges, and opportunities in pancreatic cancer. Cancer Biol Med. 2025; 22: 762-88.
53. Wei SC, Duffy CR, Allison JP. Fundamental mechanisms of immune checkpoint blockade therapy. Cancer Discov. 2018; 8: 1069-86.

54. Hallin J, Bowcut V, Calinisan A, Briere DM, Hargis L, Engstrom LD, et al. Anti-tumor efficacy of a potent and selective non-covalent KRAS^{G12D} inhibitor. Nat Med. 2022; 28: 2171-82.
55. Rajilić-Stojanović M, de Vos WM. The first 1000 cultured species of the human gastrointestinal microbiota. FEMS Microbiol Rev. 2014; 38: 996-1047.
56. Lozupone CA, Stombaugh JI, Gordon JI, Jansson JK, Knight R. Diversity, stability and resilience of the human gut microbiota. Nature. 2012; 489: 220-30.
57. Adak A, Khan MR. An insight into gut microbiota and its functionalities. Cell Mol Life Sci. 2019; 76: 473-93.
58. Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, et al. Diversity of the human intestinal microbial flora. Science. 2005; 308: 1635-8.
59. Arumugam M, Raes J, Pelletier E, Le Paslier D, Yamada T, Mende DR, et al. Enterotypes of the human gut microbiome. Nature. 2011; 473: 174-80.
60. El Aidy S, van den Bogert B, Kleerebezem M. The small intestine microbiota, nutritional modulation and relevance for health. Curr Opin Biotechnol. 2015; 32: 14-20.
61. Knights D, Ward TL, Mckinlay CE, Miller H, Gonzalez A, Mcdonald D, et al. Rethinking "enterotypes". Cell Host Microbe. 2014; 16: 433-7.
62. Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, et al. Human gut microbiome viewed across age and geography. Nature. 2012; 486: 222-7.
63. Zhang J, Guo Z, Xue Z, Sun Z, Zhang M, Wang L, et al. A phylo-functional core of gut microbiota in healthy young Chinese cohorts across lifestyles, geography and ethnicities. ISME J. 2015; 9: 1979-90.
64. Forsythe P, Bienenstock J, Kunze WA. Vagal pathways for microbiome-brain-gut axis communication. Adv Exp Med Biol. 2014; 817: 115-33.
65. O'Mahony SM, Clarke G, Borre YE, Dinan TG, Cryan JF. Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. Behav Brain Res. 2015; 277: 32-48.
66. Bayrer JR, Castro J, Venkataraman A, Touhara KK, Rossen ND, Morrie RD, et al. Gut enterochromaffin cells drive visceral pain and anxiety. Nature. 2023; 616: 137-42.
67. Ohara TE, Hsiao EY. Microbiota-neuroepithelial signalling across the gut-brain axis. Nat Rev Microbiol. 2025; 23: 371-84.
68. Lombard V, Golaconda Ramulu H, Drula E, Coutinho PM, Henrissat B. The carbohydrate-active enzymes database (CAZy) in 2013. Nucleic Acids Res. 2014; 42: D490-5.
69. Rawlings ND, Barrett AJ, Thomas PD, Huang X, Bateman A, Finn RD. The MEROPS database of proteolytic enzymes, their substrates and inhibitors in 2017 and a comparison with peptidases in the PANTHER database. Nucleic Acids Res. 2018; 46: D624-32.
70. Nicholson JK, Holmes E, Kinross J, Burcelin R, Gibson G, Jia W, et al. Host-gut microbiota metabolic interactions. Science. 2012; 336: 1262-7.
71. Selwyn FP, Csanaky IL, Zhang Y, Klaassen CD. Importance of large intestine in regulating bile acids and glucagon-like peptide-1 in germ-free mice. Drug Metab Dispos. 2015; 43: 1544-56.
72. Romano KA, Vivas EI, Amador-Noguez D, Rey FE. Intestinal microbiota composition modulates choline bioavailability from diet and accumulation of the proatherogenic metabolite trimethylamine-*N*-oxide. mBio. 2015; 6: e02481.
73. Iyer A, Soto Martín EC, Cameron GA, Louis P, Duncan SH, Bestwick CS, et al. Gorse (*Ulex europeaus*) wastes with 5,6-dimethyl benzimidazole supplementation can support growth of vitamin B12 producing commensal gut microbes. PLoS One. 2024; 19: e0290052.
74. Dalile B, Van Oudenhove L, Vervliet B, Verbeke K. The role of short-chain fatty acids in microbiota-gut-brain communication. Nat Rev Gastroenterol Hepatol. 2019; 16: 461-78.
75. Neish AS. Microbes in gastrointestinal health and disease. Gastroenterology. 2009; 136: 65-80.
76. Magalhaes JG, Tattoli I, Girardin SE. The intestinal epithelial barrier: how to distinguish between the microbial flora and pathogens. Semin Immunol. 2007; 19: 106-15.
77. Artis D. Epithelial-cell recognition of commensal bacteria and maintenance of immune homeostasis in the gut. Nat Rev Immunol. 2008; 8: 411-20.
78. Arvans DL, Vavricka SR, Ren H, Musch MW, Kang L, Rocha FG, et al. Luminal bacterial flora determines physiological expression of intestinal epithelial cytoprotective heat shock proteins 25 and 72. Am J Physiol Gastrointest Liver Physiol. 2005; 288: G696-704.
79. Aoyama M, Kotani J, Usami M. Butyrate and propionate induced activated or non-activated neutrophil apoptosis via HDAC inhibitor activity but without activating GPR-41/GPR-43 pathways. Nutrition. 2010; 26: 653-61.
80. Hayes CL, Dong J, Galipeau HJ, Jury J, Mccarville J, Huang X, et al. Commensal microbiota induces colonic barrier structure and functions that contribute to homeostasis. Sci Rep. 2018; 8: 14184.
81. Jakobsson HE, Rodríguez-Piñeiro AM, Schütte A, Ermund A, Boysen P, Bemark M, et al. The composition of the gut microbiota shapes the colon mucus barrier. EMBO Rep. 2015; 16: 164-77.
82. Singh RK, Chang HW, Yan D, Lee KM, Ucmak D, Wong K, et al. Influence of diet on the gut microbiome and implications for human health. J Transl Med. 2017; 15: 73.
83. Sen P, Molinero-Perez A, O'Riordan KJ, Mccafferty CP, O'Halloran KD, Cryan JF. Microbiota and sleep: awakening the gut feeling. Trends Mol Med. 2021; 27: 935-45.
84. Clarke SF, Murphy EF, O'Sullivan O, Lucey AJ, Humphreys M, Hogan A, et al. Exercise and associated dietary extremes impact on gut microbial diversity. Gut. 2014; 63: 1913-20.
85. Song M, Chan AT. Environmental factors, gut microbiota, and colorectal cancer prevention. Clin Gastroenterol Hepatol. 2019; 17: 275-89.
86. Sarathy J, Detloff SJ, Ao M, Khan N, French S, Sirajuddin H, et al. The Yin and Yang of bile acid action on tight junctions in a model colonic epithelium. Physiol Rep. 2017; 5: e13294.
87. Collins SL, Stine JG, Bisanz JE, Okafor CD, Patterson AD. Bile acids and the gut microbiota: metabolic interactions and impacts on disease. Nat Rev Microbiol. 2023; 21: 236-47.

88. Aburto MR, Cryan JF. Gastrointestinal and brain barriers: unlocking gates of communication across the microbiota-gut-brain axis. Nat Rev Gastroenterol Hepatol. 2024; 21: 222-47.
89. Heidari MH, Porghasem M, Mirzaei N, Mohseni JH, Heidari M, Azargashb E, et al. The effect of high level natural ionizing radiation on expression of PSA, CA19-9 and CEA tumor markers in blood serum of inhabitants of Ramsar, Iran. J Environ Radioact. 2014; 128: 64-7.
90. Uslu S, Alaca N, Kilic KD, Uysal A, Kurtel H. The effects of aerobic exercise frequencies on liver fibrosis, α-fetoprotein and cytokeratin 19 in experimental type 2 diabetes-induced rats: an immunohistochemistry study. Biotech Histochem. 2018; 93: 615-22.
91. Castelletti N, Kaiser JC, Simonetto C, Furukawa K, Küchenhoff H, Stathopoulos GT. Risk of lung adenocarcinoma from smoking and radiation arises in distinct molecular pathways. Carcinogenesis. 2019; 40: 1240-50.
92. Moldvay J, Tímár J. KRASG12C mutant lung adenocarcinoma: unique biology, novel therapies and new challenges. Pathol Oncol Res. 2023; 29: 1611580.
93. Ley RE, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. Proc Natl Acad Sci U S A. 2005; 102: 11070-5.
94. Geng J, Ni Q, Sun W, Li L, Feng X. The links between gut microbiota and obesity and obesity related diseases. Biomed Pharmacother. 2022; 147: 112678.
95. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006; 444: 1027-31.
96. Qin N, Yang F, Li A, Prifti E, Chen Y, Shao L, et al. Alterations of the human gut microbiome in liver cirrhosis. Nature. 2014; 513: 59-64.
97. Lv LX, Fang DQ, Shi D, Chen DY, Yan R, Zhu YX, et al. Alterations and correlations of the gut microbiome, metabolism and immunity in patients with primary biliary cirrhosis. Environ Microbiol. 2016; 18: 2272-86.
98. Yu LX, Schwabe RF. The gut microbiome and liver cancer: mechanisms and clinical translation. Nat Rev Gastroenterol Hepatol. 2017; 14: 527-39.
99. Clemente JC, Ursell LK, Parfrey LW, Knight R. The impact of the gut microbiota on human health: an integrative view. Cell. 2012; 148: 1258-70.
100. Shan Y, Lee M, Chang EB. The gut microbiome and inflammatory bowel diseases. Annu Rev Med. 2022; 73: 455-68.
101. Yang G, Wei J, Liu P, Zhang Q, Tian Y, Hou G, et al. Role of the gut microbiota in type 2 diabetes and related diseases. Metabolism. 2021; 117: 154712.
102. Nauck MA, Quast DR, Wefers J, Pfeiffer AFH. The evolving story of incretins (GIP and GLP-1) in metabolic and cardiovascular disease: a pathophysiological update. Diabetes Obes Metab. 2021; 23: 5-29.
103. Jiang Y, Yang J, Xia L, Wei T, Cui X, Wang D, et al. Gut microbiota-tryptophan metabolism-GLP-1 axis participates in β-cell regeneration induced by dapagliflozin. Diabetes. 2024; 73: 926-40.
104. Chen Q, Gao Y, Li F, Yuan L. The role of gut–islet axis in pancreatic islet function and glucose homeostasis. Diabetes Obes Metab. 2025; 27: 1676-92.
105. Long A, Wang Y, Guo Y, Hong J, Ning G, Meng Z, et al. A famsin-glucagon axis mediates glucose homeostasis. Cell Metab. 2025; 37: 629-39.e6.
106. Liu R, Zhang J, Chen S, Xiao Y, Hu J, Zhou Z, et al. Intestinal mucosal immunity and type 1 diabetes: non-negligible communication between gut and pancreas. Diabetes Obes Metab. 2025; 27: 1045-64.
107. Biragyn A, Ferrucci L. Gut dysbiosis: a potential link between increased cancer risk in ageing and inflammaging. Lancet Oncol. 2018; 19: e295-304.
108. Zhao J, Yang Y, Xu H, Zheng J, Shen C, Chen T, et al. Data-independent acquisition boosts quantitative metaproteomics for deep characterization of gut microbiota. NPJ Biofilms Microbiomes. 2023; 9: 4.
109. Świdnicka-Siergiejko A, Daniluk J, Miniewska K, Daniluk U, Guzińska-Ustymowicz K, Pryczynicz A, et al. Inflammatory stimuli and fecal microbiota transplantation accelerate pancreatic carcinogenesis in transgenic mice, accompanied by changes in the microbiota composition. Cells. 2025; 14: 361.
110. Yang J, Ma Y, Tan Q, Zhou B, Yu D, Jin M, et al. Gut *Streptococcus* is a microbial marker for the occurrence and liver metastasis of pancreatic cancer. Front Microbiol. 2023; 14: 1184869.
111. Su Q, Jin C, Bo Z, Yang Y, Wang J, Wang J, et al. Association between gut microbiota and gastrointestinal cancer: a two-sample bi-directional Mendelian randomization study. Front Microbiol. 2023; 14: 1181328.
112. Half E, Keren N, Reshef L, Dorfman T, Lachter I, Kluger Y, et al. Fecal microbiome signatures of pancreatic cancer patients. Sci Rep. 2019; 9: 16801.
113. Sammallahti H, Rezasoltani S, Pekkala S, Kokkola A, Asadzadeh Agdaei H, Azizmohammad Looha M, et al. Fecal profiling reveals a common microbial signature for pancreatic cancer in Finnish and Iranian cohorts. Gut Pathog. 2025; 17: 24.
114. Mekapogu AR, Xu Z, Pothula S, Perera C, Pang T, Hosen SMZ, et al. HGF/c-Met pathway inhibition combined with chemotherapy increases cytotoxic T-cell infiltration and inhibits pancreatic tumour growth and metastasis. Cancer Lett. 2023; 568: 216286.
115. Nagata N, Nishijima S, Kojima Y, Hisada Y, Imbe K, Miyoshi-Akiyama T, et al. Metagenomic identification of microbial signatures predicting pancreatic cancer from a multinational study. Gastroenterology. 2022; 163: 222-38.
116. Chen T, Li X, Li G, Liu Y, Huang X, Ma W, et al. Alterations of commensal microbiota are associated with pancreatic cancer. Int J Biol Markers. 2023; 38: 89-98.
117. Chen Y, Nian F, Chen J, Jiang Q, Yuan T, Feng H, et al. Metagenomic microbial signatures for noninvasive detection of pancreatic cancer. Biomedicines. 2025; 13: 1000.
118. Kartal E, Schmidt TSB, Molina-Montes E, Rodríguez-Perales S, Wirbel J, Maistrenko OM, et al. A faecal microbiota signature with high specificity for pancreatic cancer. Gut. 2022; 71: 1359-72.

119. Sidiropoulos T, Dovrolis N, Katifelis H, Michalopoulos NV, Kokoropoulos P, Arkadopoulos N, et al. Dysbiosis signature of fecal microbiota in patients with pancreatic adenocarcinoma and pancreatic intraductal papillary mucinous neoplasms. Biomedicines. 2024; 12: 1040.
120. Mukhopadhya I, Louis P. Gut microbiota-derived short-chain fatty acids and their role in human health and disease. Nat Rev Microbiol. 2025; 23: 635-51.
121. Matsukawa H, Iida N, Kitamura K, Terashima T, Seishima J, Makino I, et al. Dysbiotic gut microbiota in pancreatic cancer patients form correlation networks with the oral microbiota and prognostic factors. Am J Cancer Res. 2021; 11: 3163-75.
122. Xiao X, Zhang X, Wang J, Liu Y, Yan H, Xing X, et al. Proton pump inhibitors alter gut microbiota by promoting oral microbiota translocation: a prospective interventional study. Gut. 2024; 73: 1098-109.
123. Zhu J, Sun C, Li M, Hu G, Zhao XM, Chen WH. Compared to histamine-2 receptor antagonist, proton pump inhibitor induces stronger oral-to-gut microbial transmission and gut microbiome alterations: a randomised controlled trial. Gut. 2024; 73: 1087-97.
124. Schumacher J, Müller P, Sulzer J, Faber F, Molitor B, Maier L. Proton-pump inhibitors increase *C. difficile* infection risk by altering pH rather than by affecting the gut microbiome based on a bioreactor model. Gut Microbes. 2025; 17: 2519697.
125. Maier L, Pruteanu M, Kuhn M, Zeller G, Telzerow A, Anderson EE, et al. Extensive impact of non-antibiotic drugs on human gut bacteria. Nature. 2018; 555: 623-8.
126. Li H, Li C, Ren M, Zhang F, Cao L, Ren K, et al. Fasting-mimicking diet prevents pancreatic carcinogenesis via gut microbiota and metabolites. J Agric Food Chem. 2024; 72: 25638-47.
127. Vital M, Howe AC, Tiedje JM. Revealing the bacterial butyrate synthesis pathways by analyzing (meta)genomic data. mBio. 2014; 5: e00889.
128. Liang Y, Du M, Li X, Gao J, Li Q, Li H, et al. Upregulation of *Lactobacillus spp.* in gut microbiota as a novel mechanism for environmental eustress-induced anti-pancreatic cancer effects. Gut Microbes. 2025; 17: 2470372.
129. Luo B, An Q, Lei J, Tan D, Liu X, Li H, et al. Resveratrol amplifies the anti-tumor effect of α-PD-1 by altering the intestinal microbiome and PGD2 content. Gut Microbes. 2025; 17: 2447821.
130. Mizrahi JD, Surana R, Valle JW, Shroff RT. Pancreatic cancer. Lancet. 2020; 395: 2008-20.
131. Klein AP. Pancreatic cancer epidemiology: understanding the role of lifestyle and inherited risk factors. Nat Rev Gastroenterol Hepatol. 2021; 18: 493-502.
132. de Vos WM, Tilg H, Van Hul M, Cani PD. Gut microbiome and health: mechanistic insights. Gut. 2022; 71: 1020-32.
133. Fricker M, Goggins BJ, Mateer S, Jones B, Kim RY, Gellatly SL, et al. Chronic cigarette smoke exposure induces systemic hypoxia that drives intestinal dysfunction. JCI Insight. 2018; 3: e94040.
134. Hsu CL, Schnabl B. The gut–liver axis and gut microbiota in health and liver disease. Nat Rev Microbiol. 2023; 21: 719-33.
135. Akshintala VS, Talukdar R, Singh VK, Goggins M. The gut microbiome in pancreatic disease. Clin Gastroenterol Hepatol. 2019; 17: 290-5.
136. Huang JY, Luu HN, Butler LM, Midttun Ø, Ulvik A, Wang R, et al. A prospective evaluation of serum methionine-related metabolites in relation to pancreatic cancer risk in two prospective cohort studies. Int J Cancer. 2020; 147: 1917-27.
137. Mendez R, Kesh K, Arora N, Di Martino L, McAllister F, Merchant N, et al. Microbial dysbiosis and polyamine metabolism as predictive markers for early detection of pancreatic cancer. Carcinogenesis. 2020; 41: 561-70.
138. Li G, Liu L, Lu T, Sui Y, Zhang C, Wang Y, et al. Gut microbiota aggravates neutrophil extracellular traps-induced pancreatic injury in hypertriglyceridemic pancreatitis. Nat Commun. 2023; 14: 6179.
139. Qi-Xiang M, Yang F, Ze-Hua H, Nuo-Ming Y, Rui-Long W, Bin-Qiang X, et al. Intestinal TLR4 deletion exacerbates acute pancreatitis through gut microbiota dysbiosis and Paneth cells deficiency. Gut Microbes. 2022; 14: 2112882.
140. Chandra V, Li L, Le Roux O, Zhang Y, Howell RM, Rupani DN, et al. Gut epithelial Interleukin-17 receptor A signaling can modulate distant tumors growth through microbial regulation. Cancer Cell. 2024; 42: 85-100.e6.
141. Thomas RM, Gharaibeh RZ, Gauthier J, Beveridge M, Pope JL, Guijarro MV, et al. Intestinal microbiota enhances pancreatic carcinogenesis in preclinical models. Carcinogenesis. 2018; 39: 1068-78.
142. Vietsch EE, Latifi D, Verheij M, van der Oost EWA, de Wilde RF, Haen R, et al. B cell immune profiles in dysbiotic vermiform appendixes of pancreatic cancer patients. Front Immunol. 2023; 14: 1230306.
143. Morrison DJ, Preston T. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. Gut Microbes. 2016; 7: 189-200.
144. Louis P, Solvang M, Duncan SH, Walker AW, Mukhopadhya I. Dietary fibre complexity and its influence on functional groups of the human gut microbiota. Proc Nutr Soc. 2021; 80: 386-97.
145. Zhou W, Zhang D, Li Z, Jiang H, Li J, Ren R, et al. The fecal microbiota of patients with pancreatic ductal adenocarcinoma and autoimmune pancreatitis characterized by metagenomic sequencing. J Transl Med. 2021; 19: 215.
146. Sono M, Iimori K, Nagao M, Ogawa S, Maruno T, Nakanishi Y, et al. Reduction of butyrate-producing bacteria in the gut microbiome of Japanese patients with pancreatic cancer. Pancreatology. 2024; 24: 1031-9.
147. Michálková L, Horník Š, Sýkora J, Habartová L, Setnička V, Bunganič B. Early detection of pancreatic cancer in type 2 diabetes mellitus patients based on ^{1}H NMR metabolomics. J Proteome Res. 2021; 20: 1744-53.
148. O'Keefe SJ. Diet, microorganisms and their metabolites, and colon cancer. Nat Rev Gastroenterol Hepatol. 2016; 13: 691-706.
149. Li G, Lin J, Zhang C, Gao H, Lu H, Gao X, et al. Microbiota metabolite butyrate constrains neutrophil functions and

ameliorates mucosal inflammation in inflammatory bowel disease. Gut Microbes. 2021; 13: 1968257.
150. Sun Q, Ye Z, Qin Y, Fan G, Ji S, Zhuo Q, et al. Oncogenic function of TRIM2 in pancreatic cancer by activating ROS-related NRF2/ITGB7/FAK axis. Oncogene. 2020; 39: 6572-88.
151. Wang G, Gao H, Dai S, Li M, Gao Y, Yin L, et al. Metformin inhibits neutrophil extracellular traps-promoted pancreatic carcinogenesis in obese mice. Cancer Lett. 2023; 562: 216155.
152. Chang PV, Hao L, Offermanns S, Medzhitov R. The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition. Proc Natl Acad Sci U S A. 2014; 111: 2247-52.
153. Arpaia N, Campbell C, Fan X, Dikiy S, van der Veeken J, deRoos P, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. Nature. 2013; 504: 451-5.
154. Bachem A, Makhlouf C, Binger KJ, de Souza DP, Tull D, Hochheiser K, et al. Microbiota-derived short-chain fatty acids promote the memory potential of antigen-activated $CD8^+$ T cells. Immunity. 2019; 51: 285-97.e5.
155. Luu M, Riester Z, Baldrich A, Reichardt N, Yuille S, Busetti A, et al. Microbial short-chain fatty acids modulate $CD8^+$ T cell responses and improve adoptive immunotherapy for cancer. Nat Commun. 2021; 12: 4077.
156. Wang H, Chen J, Chen X, Liu Y, Wang J, Meng Q, et al. Cancer-associated fibroblasts expressing sulfatase 1 facilitate VEGFA-dependent microenvironmental remodeling to support colorectal cancer. Cancer Res. 2024; 84: 3371-87.
157. Folkerts J, Redegeld F, Folkerts G, Blokhuis B, van den Berg MPM, de Bruijn MJW, et al. Butyrate inhibits human mast cell activation via epigenetic regulation of FcεRI-mediated signaling. Allergy. 2020; 75: 1966-78.
158. Niu N, Shen X, Wang Z, Chen Y, Weng Y, Yu F, et al. Tumor cell-intrinsic epigenetic dysregulation shapes cancer-associated fibroblasts heterogeneity to metabolically support pancreatic cancer. Cancer Cell. 2024; 42: 869-84.e9.
159. Alashkar Alhamwe B, Ponath V, Alhamdan F, Dörsam B, Landwehr C, Linder M, et al. BAG6 restricts pancreatic cancer progression by suppressing the release of IL33-presenting extracellular vesicles and the activation of mast cells. Cell Mol Immunol. 2024; 21: 918-31.
160. Estival A, Clerc P, Vaysse N, Tam JP, Clemente F. Decreased expression of transforming growth factor alpha during differentiation of human pancreatic cancer cells. Gastroenterology. 1992; 103: 1851-9.
161. Zhang JS, Wang L, Huang H, Nelson M, Smith DI. Keratin 23 (K23), a novel acidic keratin, is highly induced by histone deacetylase inhibitors during differentiation of pancreatic cancer cells. Genes Chromosomes Cancer. 2001; 30: 123-35.
162. Pushalkar S, Hundeyin M, Daley D, Zambirinis CP, Kurz E, Mishra A, et al. The pancreatic cancer microbiome promotes oncogenesis by induction of innate and adaptive immune suppression. Cancer Discov. 2018; 8: 403-16.
163. Malhotra P, Palanisamy R, Caparros-Martin JA, Falasca M. Bile acids and microbiota interplay in pancreatic cancer. Cancers (Basel). 2023; 15: 3573.
164. Riquelme E, Zhang Y, Zhang L, Montiel M, Zoltan M, Dong W, et al. Tumor microbiome diversity and composition influence pancreatic cancer outcomes. Cell. 2019; 178: 795-806.e12.
165. Halimi A, Gabarrini G, Sobkowiak MJ, Ateeb Z, Davanian H, Gaiser RA, et al. Isolation of pancreatic microbiota from cystic precursors of pancreatic cancer with intracellular growth and DNA damaging properties. Gut Microbes. 2021; 13: 1983101.
166. Geller LT, Barzily-Rokni M, Danino T, Jonas OH, Shental N, Nejman D, et al. Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine. Science. 2017; 357: 1156-60.
167. Aykut B, Pushalkar S, Chen R, Li Q, Abengozar R, Kim JI, et al. The fungal mycobiome promotes pancreatic oncogenesis via activation of MBL. Nature. 2019; 574: 264-7.
168. Fritz S, Hackert T, Hartwig W, Rossmanith F, Strobel O, Schneider L, et al. Bacterial translocation and infected pancreatic necrosis in acute necrotizing pancreatitis derives from small bowel rather than from colon. Am J Surg. 2010; 200: 111-7.
169. Diehl GE, Longman RS, Zhang JX, Breart B, Galan C, Cuesta A, et al. Microbiota restricts trafficking of bacteria to mesenteric lymph nodes by CX_3CR1^{hi} cells. Nature. 2013; 494: 116-20.
170. Thomas RM, Jobin C. Microbiota in pancreatic health and disease: the next frontier in microbiome research. Nat Rev Gastroenterol Hepatol. 2020; 17: 53-64.
171. Yu Q, Newsome RC, Beveridge M, Hernandez MC, Gharaibeh RZ, Jobin C, et al. Intestinal microbiota modulates pancreatic carcinogenesis through intratumoral natural killer cells. Gut Microbes. 2022; 14: 2112881.
172. Tabrizi E, Pourteymour Fard Tabrizi F, Mahmoud Khaled G, Sestito MP, Jamie S, Boone BA. Unraveling the gut microbiome's contribution to pancreatic ductal adenocarcinoma: mechanistic insights and therapeutic perspectives. Front Immunol. 2024; 15: 1434771.
173. Ikebe M, Kitaura Y, Nakamura M, Tanaka H, Yamasaki A, Nagai S, et al. Lipopolysaccharide (LPS) increases the invasive ability of pancreatic cancer cells through the TLR4/MyD88 signaling pathway. J Surg Oncol. 2009; 100: 725-31.
174. Yin H, Pu N, Chen Q, Zhang J, Zhao G, Xu X, et al. Gut-derived lipopolysaccharide remodels tumoral microenvironment and synergizes with PD-L1 checkpoint blockade via TLR4/MyD88/AKT/NF-κB pathway in pancreatic cancer. Cell Death Dis. 2021; 12: 1033.
175. Sethi V, Kurtom S, Tarique M, Lavania S, Malchiodi Z, Hellmund L, et al. Gut microbiota promotes tumor growth in mice by modulating immune response. Gastroenterology. 2018; 155: 33-7.e6.
176. Li Y, Chang RB, Stone ML, Delman D, Markowitz K, Xue Y, et al. Multimodal immune phenotyping reveals microbial-T cell interactions that shape pancreatic cancer. Cell Rep Med. 2024; 5: 101397.

177. Halbrook CJ, Lyssiotis CA, Pasca Di Magliano M, Maitra A. Pancreatic cancer: advances and challenges. Cell. 2023; 186: 1729-54.
178. Choy ATF, Carnevale I, Coppola S, Meijer LL, Kazemier G, Zaura E, et al. The microbiome of pancreatic cancer: from molecular diagnostics to new therapeutic approaches to overcome chemoresistance caused by metabolic inactivation of gemcitabine. Expert Rev Mol Diagn. 2018; 18: 1005-9.
179. Kesh K, Mendez R, Mateo-Victoriano B, Garrido VT, Durden B, Gupta VK, et al. Obesity enriches for tumor protective microbial metabolites and treatment refractory cells to confer therapy resistance in PDAC. Gut Microbes. 2022; 14: 2096328.
180. Kesh K, Mendez R, Abdelrahman L, Banerjee S, Banerjee S. Type 2 diabetes induced microbiome dysbiosis is associated with therapy resistance in pancreatic adenocarcinoma. Microb Cell Fact. 2020; 19: 75.
181. Sivan A, Corrales L, Hubert N, Williams JB, Aquino-Michaels K, Earley ZM, et al. Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy. Science. 2015; 350: 1084-9.
182. Vétizou M, Pitt JM, Daillère R, Lepage P, Waldschmitt N, Flament C, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Science. 2015; 350: 1079-84.
183. Fessler J, Matson V, Gajewski TF. Exploring the emerging role of the microbiome in cancer immunotherapy. J Immunother Cancer. 2019; 7: 108.
184. Xing H, Wang J, Wang Y, Tong M, Hu H, Huang C, et al. Diagnostic value of CA 19-9 and carcinoembryonic antigen for pancreatic cancer: a meta-analysis. Gastroenterol Res Pract. 2018; 2018: 8704751.
185. Takaori A, Hashimoto D, Ikeura T, Ito T, Nakamaru K, Masuda M, et al. Impact of neoadjuvant therapy on gut microbiome in patients with resectable/borderline resectable pancreatic ductal adenocarcinoma. Pancreatology. 2023; 23: 367-76.
186. Raman M, Ambalam P, Kondepudi KK, Pithva S, Kothari C, Patel AT, et al. Potential of probiotics, prebiotics and synbiotics for management of colorectal cancer. Gut Microbes. 2013; 4: 181-92.
187. Song Q, Zhang X, Liu W, Wei H, Liang W, Zhou Y, et al. *Bifidobacterium pseudolongum*-generated acetate suppresses non-alcoholic fatty liver disease-associated hepatocellular carcinoma. J Hepatol. 2023; 79: 1352-65.
188. Lee TS. Are probiotics beneficial or harmful for pancreatic cancer outcomes? Probiotics Antimicrob Proteins. 2025; 17: 2293-300.
189. Panebianco C, Pisati F, Ulaszewska M, Andolfo A, Villani A, Federici F, et al. Tuning gut microbiota through a probiotic blend in gemcitabine-treated pancreatic cancer xenografted mice. Clin Transl Med. 2021; 11: e580.
190. Panebianco C, Pisati F, Villani A, Andolfo A, Ulaszewska M, Bellini E, et al. Counteracting gemcitabine+nab-paclitaxel induced dysbiosis in KRAS wild type and $KRAS^{G12D}$ mutated pancreatic cancer in vivo model. Cell Death Discov. 2023; 9: 116.
191. Kaur K, Kozlowska AK, Topchyan P, Ko MW, Ohanian N, Chiang J, et al. Probiotic-treated super-charged NK cells efficiently clear poorly differentiated pancreatic tumors in Hu-BLT mice. Cancers (Basel). 2019; 12: 63.
192. Maher S, Elmeligy HA, Aboushousha T, Helal NS, Ossama Y, Rady M, et al. Synergistic immunomodulatory effect of synbiotics pre- and postoperative resection of pancreatic ductal adenocarcinoma: a randomized controlled study. Cancer Immunol Immunother. 2024; 73: 109.
193. Chen SM, Chieng WW, Huang SW, Hsu LJ, Jan MS. The synergistic tumor growth-inhibitory effect of probiotic *Lactobacillus* on transgenic mouse model of pancreatic cancer treated with gemcitabine. Sci Rep. 2020; 10: 20319.
194. Chaib M, Hafeez BB, Mandil H, Daria D, Pingili AK, Kumari S, et al. Reprogramming of pancreatic adenocarcinoma immunosurveillance by a microbial probiotic siderophore. Commun Biol. 2022; 5: 1181.
195. Zhu Z, Yi B, Tang Z, Chen X, Li M, Xu T, et al. *Lactobacillus casei* combined with *Lactobacillus reuteri* alleviate pancreatic cancer by inhibiting TLR4 to promote macrophage M1 polarization and regulate gut microbial homeostasis. BMC Cancer. 2023; 23: 1044.
196. Kita A, Fujiya M, Konishi H, Tanaka H, Kashima S, Iwama T, et al. Probiotic-derived ferrichrome inhibits the growth of refractory pancreatic cancer cells. Int J Oncol. 2020; 57: 721-32.
197. Han ZY, Fu ZJ, Wang YZ, Zhang C, Chen QW, An JX, et al. Probiotics functionalized with a gallium-polyphenol network modulate the intratumor microbiota and promote anti-tumor immune responses in pancreatic cancer. Nat Commun. 2024; 15: 7096.
198. Yang X, Zhang Z, Shen X, Xu J, Weng Y, Wang W, et al. *Clostridium butyricum* and its metabolite butyrate promote ferroptosis susceptibility in pancreatic ductal adenocarcinoma. Cell Oncol (Dordr). 2023; 46: 1645-58.
199. Yao WQ, Song WF, Deng XC, Lin YT, Meng R, Wang JW, et al. Harnessing the engineered probiotic-nanosystem to remodulate tumor extracellular matrix and regulate tumor-colonizing bacteria for improving pancreatic cancer chemo-immunotherapy. Small. 2025; 21: e2406837.
200. Swanson KS, Gibson GR, Hutkins R, Reimer RA, Reid G, Verbeke K, et al. The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of synbiotics. Nat Rev Gastroenterol Hepatol. 2020; 17: 687-701.
201. Rayes N, Seehofer D, Theruvath T, Mogl M, Langrehr JM, Nüssler NC, et al. Effect of enteral nutrition and synbiotics on bacterial infection rates after pylorus-preserving pancreatoduodenectomy: a randomized, double-blind trial. Ann Surg. 2007; 246: 36-41.
202. Smits LP, Bouter KE, de Vos WM, Borody TJ, Nieuwdorp M. Therapeutic potential of fecal microbiota transplantation. Gastroenterology. 2013; 145: 946-53.
203. Wang X, Fang Y, Liang W, Wong CC, Qin H, Gao Y, et al. *Fusobacterium nucleatum* facilitates anti-PD-1 therapy in microsatellite stable colorectal cancer. Cancer Cell. 2024; 42: 1729-46.e8.
204. Baruch EN, Youngster I, Ben-Betzalel G, Ortenberg R, Lahat A, Katz L, et al. Fecal microbiota transplant promotes response in

immunotherapy-refractory melanoma patients. Science. 2021; 371: 602-9.
205. Tintelnot J, Xu Y, Lesker TR, Schönlein M, Konczalla L, Giannou AD, et al. Microbiota-derived 3-IAA influences chemotherapy efficacy in pancreatic cancer. Nature. 2023; 615: 168-74.
206. Panebianco C, Villani A, Pisati F, Orsenigo F, Ulaszewska M, Latiano TP, et al. Butyrate, a postbiotic of intestinal bacteria, affects pancreatic cancer and gemcitabine response in *in vitro* and *in vivo* models. Biomed Pharmacother. 2022; 151: 113163.
207. Mirji G, Worth A, Bhat SA, El Sayed M, Kannan T, Goldman AR, et al. The microbiome-derived metabolite TMAO drives immune activation and boosts responses to immune checkpoint blockade in pancreatic cancer. Sci Immunol. 2022; 7: eabn0704.
208. Nakaoka K, Ohno E, Kuramitsu K, Kuzuya T, Funasaka K, Tochio T, et al. Efficacy of 1-kestose supplementation in patients with pancreatic ductal adenocarcinoma: a randomized controlled pilot study. Nutrients. 2024; 16: 2889.
209. Cortez NE, Rodriguez Lanzi C, Hong BV, Xu J, Wang F, Chen S, et al. A ketogenic diet in combination with gemcitabine increases survival in pancreatic cancer KPC mice. Cancer Res Commun. 2022; 2: 951-65.
210. Roichman A, Zuo Q, Hwang S, Lu W, Cordova RA, MacArthur MR, et al. Microbiome metabolism of dietary phytochemicals controls the anticancer activity of PI3K inhibitors. Cell. 2025; 188: 3065-80.e21.
211. Panyod S, Wu WK, Lee YP, Lin TY, Kuo PC, Yen CS, et al. Refining antibiotic cocktail regimens for pseudo-germ-free mice and their impact on gut microbiome and pancreatic tumor proteomics. J Adv Res. Published online Aug 13, 2025. DOI: 10.1016/j.jare.2025.08.015.
212. Amisaki M, Zebboudj A, Yano H, Zhang SL, Payne G, Chandra AK, et al. IL-33-activated ILC2s induce tertiary lymphoid structures in pancreatic cancer. Nature. 2025; 638: 1076-84.
213. Cheng AG, Ho PY, Aranda-Díaz A, Jain S, Yu FB, Meng X, et al. Design, construction, and *in vivo* augmentation of a complex gut microbiome. Cell. 2022; 185: 3617-36.e19.
214. Cheng WY, Wu CY, Yu J. The role of gut microbiota in cancer treatment: friend or foe? Gut. 2020; 69: 1867-76.
215. DeLeon O, Mocanu M, Tan A, Sidebottom AM, Koval J, Ceccato HD, et al. Microbiome mismatches from microbiota transplants lead to persistent off-target metabolic and immunomodulatory effects. Cell. 2025; 188: 3927-41.e13.
216. Lloréns-Rico V, Simcock JA, Huys GRB, Raes J. Single-cell approaches in human microbiome research. Cell. 2022; 185: 2725-38.
217. Venturelli OS, Carr AC, Fisher G, Hsu RH, Lau R, Bowen BP, et al. Deciphering microbial interactions in synthetic human gut microbiome communities. Mol Syst Biol. 2018; 14: e8157.
218. Marsh JW, Ley RE. Microbiome engineering: taming the untractable. Cell. 2022; 185: 416-8.

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