Microbiota in pancreatic cancer: Roles in tumor initiation and progression (Review)

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Abstract. Pancreatic cancer is a highly aggressive malignancy with limited therapeutic options and poor survival outcomes, highlighting the need for an improved understanding of its underlying biology. Advances have positioned the human microbiome as a critical regulator of the initiation and progression of pancreatic cancer. Microbial communities across the oral-gut-tumor axis contribute to tumor initiation through coordinated mechanisms, including the induction of genotoxic stress, chronic inflammation and activation of oncogenic signaling pathways. During tumor progression, microbiota dynamically shape the tumor microenvironment by modulating immune responses, metabolic reprogramming and stromal remodeling. Notably, microbial influences are bidirectional, as tumor-promoting and tumor-suppressive taxa exert opposing effects that converge on shared regulatory pathways within the tumor ecosystem. The present study reviews the current understanding of microbiome involvement in pancreatic cancer, focusing on its mechanistic roles in tumor initiation and progression. Furthermore, the key challenges in the field are discussed, and the emerging opportunities for therapeutic intervention are highlighted. These insights provide a conceptual framework for integrating microbiome research into precision oncology for pancreatic cancer.

Contents

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1. Introduction

Pancreatic cancer represents one of the most lethal oncological malignancies, characterized by a poor prognosis that has remained largely unchanged over the past several years (1-3). According to GLOBOCAN 2022, pancreatic cancer accounted for ~510,566 new cases and 467,005 deaths worldwide, ranking 12th in incidence and 6th in mortality among all cancers globally. The age-standardized incidence rate (ASR) was 5.5 per 100,000 in men and 4.0 per 100,000 in women, while the corresponding mortality rates were 5.0 and 3.5 per 100,000, respectively (4).

The global burden of pancreatic cancer exhibits substantial geographic variation. The highest ASRs per 100,000 individuals of both sexes are observed in Uruguay (11.4), Hungary (10.4), Japan (9.8), Austria (9.4) and metropolitan France (9.4), whereas comparatively lower rates persist across a number of regions of South-Central Asia and sub-Saharan Africa (5). In terms of absolute case numbers, China (118,672 new cases), the United States (60,127) and Japan (47,627) bear the greatest disease burden, reflecting the combined influence of population size, population aging and the prevalence of established risk factors, such as pancreatitis, cigarette smoking, heavy alcohol consumption, diabetes and obesity (5). Mortality-to-incidence ratios remain high across all regions, with the leading mortality ASRs per 100,000 individuals reported in Germany (8.2), Japan (8.0) and metropolitan France (8.0) (5). In the United States, pancreatic cancer is estimated to account for ~3.2% of all newly diagnosed cancer cases with 67,530 new cases projected for 2026 (3). Moreover, the mortality burden is projected to increase further and pancreatic cancer is projected to become the second leading cause of cancer-related death by 2030 (6).

The poor clinical outcomes associated with pancreatic cancer are fundamentally linked to its biological behavior and diagnostic challenges. Only 15% of cases are identified at the localized stage, when the 5-year survival rate is 43.6%; however, the majority of patients present with distant metastatic disease, for which the 5-year survival rate reduces to 3.2% (7).

The aforementioned survival statistics reflect the advanced stage at which most patients are diagnosed, as pancreatic cancer typically exhibits minimal or no symptoms during its early phases (8), and the near-equivalence between incidence and mortality rates underscores the aggressive nature of the disease and the limited effectiveness of current therapeutic interventions (9).

Surgical resection remains the only potentially curative treatment modality for pancreatic cancer; however, only patients with localized disease are eligible for pancreatectomy at the time of diagnosis. Even among those who undergo successful margin-negative resection, the 5-year survival rate is 17-21% and up to 86% experience disease recurrence despite complete tumor removal (8,10). Therefore, pharmacological therapy serves a central role in the comprehensive management of pancreatic cancer and as a critical component throughout the entire disease course. Current systemic therapeutic approaches, including FOLFIRINOX and gemcitabine-based regimens, have achieved only modest improvements in overall survival. For advanced disease, the median overall survival time remains at <12 months, with median progression-free survival time at <8 months (11). Pancreatic ductal adenocarcinoma (PDAC), which accounts for >90% of pancreatic malignancies, is characterized by a dense desmoplastic stroma that forms a substantial physical barrier, thereby limiting drug delivery and contributing to systemic therapeutic resistance (8,12). In addition, the hypovascular nature of the tumor microenvironment (TME) further restricts the perfusion-dependent delivery of systemic agents (12). The low frequency of KRAS G12V mutations and the immunosuppressive TME, characterized by limited T-cell infiltration, explain the disappointing efficacy of target therapy and immunotherapy (13). These persistent challenges have intensified research efforts to identify novel therapeutic targets and innovative treatment paradigms.

Microbiota has emerged as a critical determinant of cancer pathogenesis, progression and therapeutic response. Over the past decade, accumulating evidence has fundamentally transformed understanding of the TME, revealing that both local and distant microbial communities actively participate in modulating oncogenic processes across multiple cancer types (14,15). The microbiota influences tumor biology through diverse mechanisms, including the induction of host DNA damage, modulation of oncogenic signaling pathways such as WNT-β-catenin, NF-κB and PI3K-AKT cascades, and orchestration of local and systemic inflammatory responses (15-19). These microbe-host interactions are bidirectional: Specific microbes can promote pro-tumorigenic niches by suppressing cytotoxic immune cells and enhancing immunosuppressive populations, whereas microbial components may also function as neoantigens or generate metabolites that potentiate antitumor immunity (20).

The gastrointestinal tract, which harbors the largest reservoir of human microbiota, is closely connected to the pancreas through the gut-pancreas axis, suggesting a potential route for microbial influence on pancreatic biology (21). Dysbiosis, characterized by perturbations in microbial composition and function, has been associated with alterations in the pancreatic tumor immune microenvironment, the promotion of chronic inflammation and the facilitation of immune evasion (22,23). As a digestive system malignancy, PDAC appears to interact with microbial communities across multiple anatomical sites, including the oral cavity, gastrointestinal tract and tumor tissue, indicating that the microbiome may serve as a candidate source of diagnostic biomarkers and therapeutic targets (24).

The present review aimed to systematically summarize current knowledge on the role of the human microbiota in pancreatic cancer, with a focus on its mechanistic contributions to tumorigenesis and therapeutic response. Microbial influences across the oral, gut and intratumoral compartments are examined, and how dysbiosis shapes the tumor immune microenvironment through immune reprogramming, metabolic interactions and microbe-microbe crosstalk is discussed. Furthermore, the potential of microbiota-derived biomarkers for early diagnosis and risk stratification, as well as emerging microbiome-targeted therapeutic strategies, is evaluated.

2. Microbiota in pancreatic cancer initiation

Pancreatic cancer initiation is a multistep process involving the accumulation of genetic and epigenetic alterations together with changes in the TME. Recent studies have suggested that microbial communities across the oral, gastrointestinal and pancreatic compartments may contribute to early carcinogenesis through mechanisms such as genomic instability, inflammation, immune modulation and metabolic reprogramming (16,25). PDAC develops over a prolonged latency period, during which precursor lesions, including pancreatic intraepithelial neoplasia, undergo stepwise progression to invasive carcinoma (26). During this phase, microbial dysbiosis has been associated with alterations in oncogenic signaling, stromal activation and the establishment of an immunosuppressive microenvironment that may facilitate neoplastic progression (21). These observations indicate a potential role for microbiota in pancreatic cancer initiation and support further investigation into their value in early detection and prevention.

Oral and intratumoral microbiome. The oral cavity harbors a diverse microbial community, some members of which have been associated with oncogenic processes. Epidemiological studies have reported consistent associations between periodontal disease and increased pancreatic cancer risk (27,28), and prospective cohort analyses have identified specific oral taxa, particularly members of the 'red' and 'orange' complexes, as being linked to disease development (28). These microorganisms may disseminate to pancreatic tissue via hematogenous or lymphatic routes, and are hypothesized to contribute to pro-tumorigenic microenvironments through virulence-associated mechanisms (27,29). *Porphyromonas gingivalis* has been frequently implicated in this context; its gingipains have been shown to regulate MMP-9 expression through NF-κB signaling, which may influence extracellular matrix remodeling and tumor invasion (30,31). In addition, the production of nucleoside diphosphate kinase enables hydrolysis of extracellular ATP and inhibition of P2X7-mediated apoptosis, a mechanism that may permit the persistence of damaged cells (32). Following cellular invasion, *P. gingivalis* has been reported to modulate ERK1/2-Ets1, p38/HSP27, JAK/STAT and AKT signaling pathways, which

may collectively contribute to enhanced cell survival under oncogenic conditions (27,33,34). *Aggregatibacter actinomycetemcomitans* produces cytolethal distending toxin, the CdtB subunit of which exhibits phosphatase activity that alters PIP3 signaling and may enhance PI3K pathway activation (35-38). Given the central role of PI3K in KRAS signaling, this mechanism may be relevant to early tumorigenesis (39-41).

The intrapancreatic microbiome is increasingly considered a distinct, low-biomass ecosystem that may become altered and metabolically active during PDAC progression (42). Although previously considered sterile, the pancreas has been shown to harbor microbial communities predominantly composed of Proteobacteria, Firmicutes, Bacteroidetes and Actinobacteria (24,43). The fungal component of the microbiome has also been implicated, with PDAC tissues exhibiting substantially increased fungal burden and distinct composition compared with normal pancreas (44). *Malassezia* species have been associated with activation of the mannose-binding lectin-complement pathway, whereby fungal glycans may induce C3 cleavage and C3a-mediated signaling, potentially promoting tumor cell proliferation and survival (44).

Gut microbiome. The gastrointestinal microbiome is increasingly recognized as a potential contributor to pancreatic cancer initiation through the gut-pancreas axis (45). Studies using metagenomic profiling have identified distinct gut microbial features in patients with PDAC, including reduced α diversity and shifts in phylum-level composition, such as increased *Bacteroides* and decreased Proteobacteria (46,47). These changes have been associated with increased levels of pro-inflammatory cytokines, including TNF-α, and may contribute to the establishment of a microenvironment permissive to tumor development (24,48). Chronic pancreatitis, a well-established risk factor for pancreatic cancer, has also been associated with gut microbiota dysbiosis, with reduced abundance of *Enterococcus faecalis* and other commensals suggesting a potential role for decreased microbial diversity in disease progression (49). In addition, small intestinal bacterial overgrowth may induce lipopolysaccharide-mediated inflammation and has been proposed to contribute to KRAS activation, particularly in the context of sustained inflammatory signaling (50).

Alterations in microbial metabolism may provide an additional mechanistic link between dysbiosis and pancreatic carcinogenesis. Reduced levels of commensal taxa such as *Faecalibacterium* and *Akkermansia* have been associated with disruptions in bile acid and tryptophan metabolic pathways, which may activate pro-inflammatory signaling and promote epithelial-mesenchymal transition (EMT) (51,52). Secondary bile acids may act as damage-associated molecular patterns, inducing reactive oxygen species (ROS) production and NF-κB activation, while microbial metabolism of tryptophan yields kynurenine derivatives that activate the aryl hydrocarbon receptor, promoting regulatory T-cell differentiation and suppressing antitumor immunity, thereby establishing an immunosuppressive environment conducive to tumor initiation (53). *Helicobacter pylori* has also been implicated in this context; chronic infection has been associated with alterations in gastric endocrine function, including reduced somatostatin secretion and increased secretin activity, which may contribute to pancreatic ductal hyperplasia (54). In addition, *H. pylori* overgrowth may promote N-nitrosamine formation and DNA damage, while the CagE protein has been reported to exhibit helicase activity and regulate DNA methylation, suggesting a potential role in mutagenesis (27). Together, these findings suggest that the gut microbiome may contribute to pancreatic cancer initiation through interconnected metabolic and immune mechanisms.

3. Microbiota in pancreatic cancer progression

The progression of pancreatic cancer from localized disease to invasive and metastatic stages is increasingly understood to be influenced by complex interactions among cancer cells, the TME and microbial communities (55). Emerging evidence has suggested that specific microbial taxa may exert dichotomous effects during disease progression, with some species potentially promoting malignant advancement and metastatic dissemination through mechanisms such as immune suppression, metabolic reprogramming and stromal remodeling, while others may inhibit tumor progression by enhancing immune activation and maintaining homeostatic barriers (56). These observations provide a conceptual framework for distinguishing metastasis-promoting and metastasis-inhibiting microbes, and highlight the importance of elucidating species-specific mechanisms to inform microbiome-based therapeutic strategies.

Tumor-promoting microbial species. Accumulating evidence has indicated that tumor-promoting microbiota facilitate pancreatic cancer progression through convergent oncogenic mechanisms, despite taxonomic diversity (15,16). *Fusobacterium nucleatum* represents a prototypical example, integrating inflammatory signaling, extracellular matrix remodeling and immune evasion (57). Through Fap2-mediated adhesion, it induces pro-tumorigenic cytokine (IL-8 and CXCL1) secretion (58), while activation of p38 MAPK signaling enhances MMP-dependent matrix degradation (47). In parallel, *F. nucleatum* suppresses antitumor immunity via TIGIT engagement and promotes metastatic communication through extracellular vesicles, collectively driving aggressive disease phenotypes (59).

A second mechanistic axis involves protease-driven signaling and cytoskeletal remodeling, exemplified by *P. gingivalis*. Notably, gingipains from *P. gingivalis* activate protease-activated receptor (PAR)2 and downstream NF-κB signaling while simultaneously enhancing p38 pathway activity, leading to increased MMP activation and invasion (60). Moreover, *P. gingivalis* modulates cytoskeletal dynamics via protein citrullination, facilitating tumor cell motility (47,61). Other bacteria, including *Klebsiella* species and *E. faecalis*, reinforce these processes by sustaining chronic inflammation, inducing DNA damage, activating inflammasomes and promoting immune escape, thereby amplifying tumor progression (45,62,63).

In addition to signaling and inflammatory pathways, microbial regulation of tumor metabolism and the microenvironment has emerged as a critical determinant of disease progression. *Pseudomonas* species are implicated in amino acid metabolism and the induction of autophagy, potentially linking

microbial activity to PI3K/AKT/mTOR signaling and tumor progression (64). *Streptococcus anginosus* further contributes through MAPK activation and proliferative signaling (65). *P. gingivalis* accelerates pancreatic cancer progression by fostering a neutrophil-dominated proinflammatory TME through enhanced secretion of neutrophilic chemokines (e.g., Cxcl1, Cxcl2, Cxcr2) and neutrophil elastase (66). These findings suggest that distinct microbial taxa converge on shared oncogenic programs, underscoring the microbiome as an integral regulator of pancreatic cancer progression.

Tumor-suppressing microbial species. In contrast to tumor-promoting microbiota, tumor-suppressive microbial species exert protective effects through convergent mechanisms centered on immune activation, metabolic regulation and maintenance of host-microbe homeostasis (67-69). *Lactobacillus* species, particularly *Lactobacillus reuteri*, exemplify this paradigm by enhancing antitumor immunity. Through promoting natural killer (NK)-cell recruitment and activation, as well as inducing M1 macrophage polarization via inhibition of Toll-like receptor (TLR)4 signaling, *Lactobacillus* strengthens innate immune responses within the TME (56,70). Additionally, microbial metabolites such as acetate further potentiate T-cell and NK-cell function, reinforcing systemic and local antitumor immunity (70).

Another key protective microbe, *Akkermansia muciniphila*, contributes to pancreatic cancer suppression through modulation of host immunity and preservation of mucosal barrier integrity (71). This mucin-degrading bacterium is enriched in long-term survivors with pancreatic cancer and is associated with a T cell-inflamed TME (72). *A. muciniphila* enhances antitumor immunity by promoting M1-like macrophage polarization, activating the NLRP3 inflammasome and increasing T-cell infiltration into tumors (73). Notably, in patient-based studies, restoration of *A. muciniphila* has been associated with improved responses to chemotherapy (71,74). However, its effects appear to be context-dependent, as excessive colonization may compromise barrier function and induce systemic inflammation (75).

Metabolic regulation constitutes an additional layer of tumor suppression. *Faecalibacterium prausnitzii* and *Bifidobacterium* species, both reduced in PDAC, produce short-chain fatty acids (SCFAs) such as butyrate that inhibit tumor proliferation, induce apoptosis and enhance immune activation (76-78). Loss of these beneficial microbes leads to impaired barrier function, reduced SCFA production and increased susceptibility to pro-tumorigenic inflammation (78). Collectively, these findings illustrate that tumor-suppressive microbiota converge on key host pathways to counteract pancreatic cancer progression, providing a conceptual framework for microbiome-based therapeutic strategies.

Microbiota-immune crosstalk in the PDAC TME. The oral-gut-tumor microbial axis may shape PDAC progression through coordinated effects on adaptive immunity, myeloid-cell function, innate sensing pathways and metabolite-mediated immune regulation. Emerging evidence has suggested that gut microbiome dysbiosis contributes to T-cell exclusion and dysfunction, whereas microbiota depletion is associated with enhanced intratumoral T-cell infiltration, reduced myeloid-derived suppressor cell (MDSC) accumulation and suppression of tumor growth in preclinical models (22,79). IL-17 appears to represent an important mechanistic link, as IL-17 neutralization abrogates the tumor-suppressive effect of antibiotic treatment, suggesting a connection between commensal-driven T helper 17 (Th17) responses and PDAC immune evasion (80,81). In parallel, PDAC-derived CCL2 recruits monocytic MDSCs and promotes acquisition of a suppressive phenotype characterized by increased ROS and arginase production, a process that may be partially dependent on MAPK signaling (82).

Microbial regulation of the PDAC immune landscape also involves tumor-intrinsic immunosuppressive programs, innate immune sensing pathways and metabolite-dependent signaling. Thrombin-PAR1 signaling has been linked to reduced cytotoxic T-cell infiltration and increased tumor-associated macrophage accumulation through upregulation of Csf2 and Ptgs2 (83). In addition, microbial products (e.g., lipopolysaccharides, flagellins) engage TLRs, cGAS-STING and NOD-like receptors, generating context-dependent effects that range from chronic tumor-promoting inflammation to type I interferon-mediated antitumor responses (22,80,84). Microbial metabolites, including SCFAs, secondary bile acids and tryptophan catabolites, may regulate inflammasome activity, chromatin accessibility, NK-cell function and T-cell differentiation (80,85-87). Furthermore, disruption of gut barrier integrity may facilitate systemic endotoxemia, promoting myeloid skewing and stromal remodeling (88).

Collectively, these observations suggest that microbiota-mediated immune regulation converges on several key pathways, including IL-17/Th17 signaling, CCL2-dependent MDSC recruitment and PAR1-associated myeloid programming. These findings raise the possibility that targeted modulation of microbial communities or their metabolites could help reprogram the PDAC TME toward more durable antitumor immunity.

4. Obesity, diabetes and the microbiome in PDAC

Impact of obesity and diabetes on PDAC. Obesity and type 2 diabetes mellitus (T2DM) are consistently associated with an elevated risk of PDAC and adverse outcomes (8). Pancreatic cancer and T2DM exhibit a bidirectional relationship, in which diabetes acts as both a risk factor and a metabolic consequence of occult pancreatic malignancy (89,90). In available epidemiological analyses, T2DM has been associated with an increased annual incidence rate of PDAC, with a standardized incidence ratio of 1.54 (95% CI, 1.45-1.64) (91). Major contributors to this association include hyperglycemia, hyperinsulinemia, pancreatitis, dyslipidemia, insulin resistance and inflammatory processes within the TME (92). Obesity may further amplify this axis by increasing circulating insulin levels, and altering leptin and adiponectin signaling (93-95).

Obesity and diabetes promote pancreatic carcinogenesis through a convergent immunometabolic program (96). Excess nutrient availability and metabolite accumulation support carcinogenesis by amplifying mutagenic and genotoxic stress, while obesity- and diabetes-associated alterations in gastrointestinal and sex-hormone signaling interact with microbiome dysfunction to foster an immunosuppressive TME (96,97).

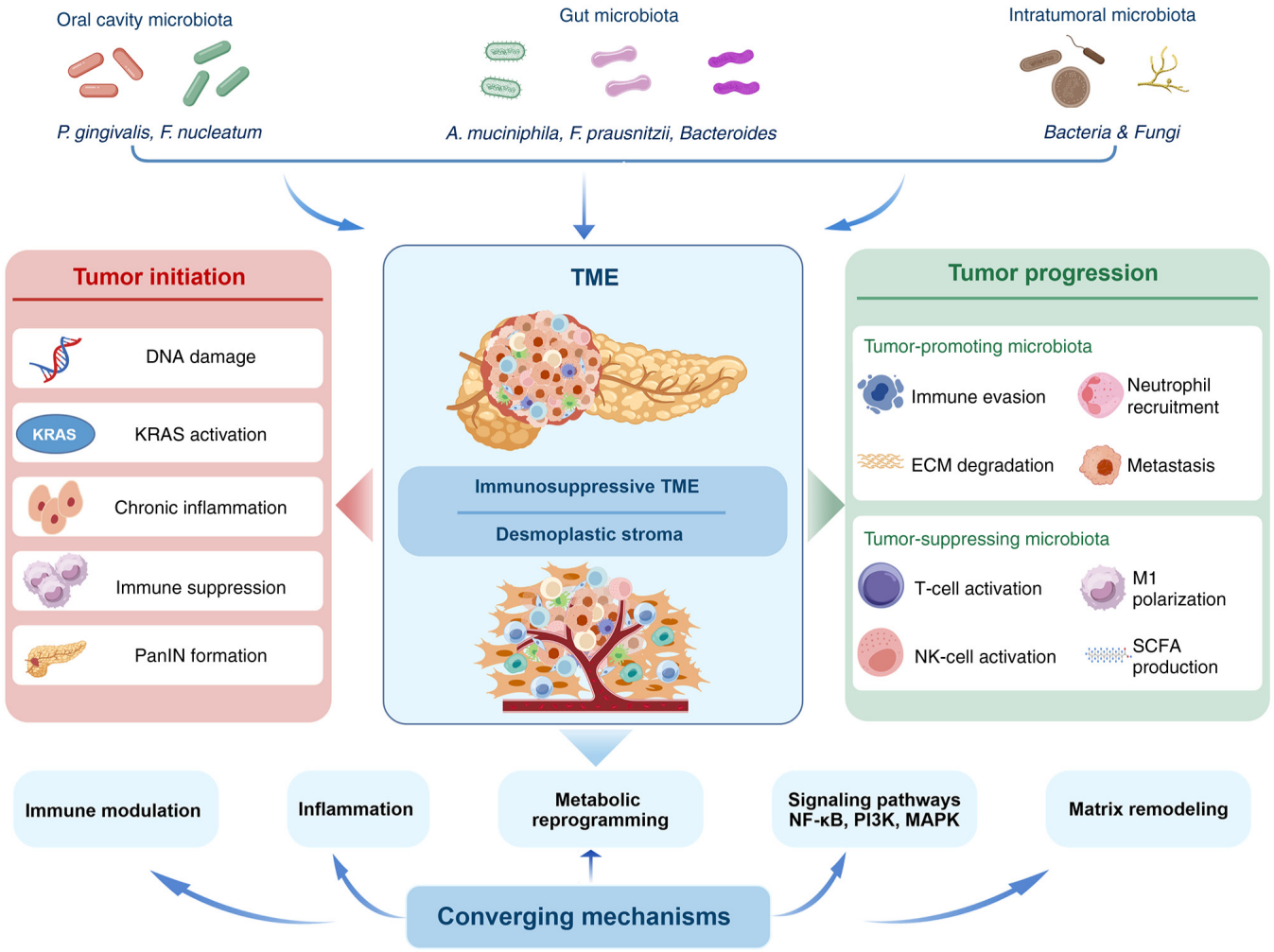

Figure 1. Microbiome-tumor interactions in pancreatic cancer initiation and progression. Oral, gut and intratumoral microbiota may promote tumor initiation through persistent activation of NF-κB signaling, induction of genotoxic stress by microbial toxins and inflammatory mediators, and activation of oncogenic pathways such as PI3K and MAPK. During disease progression, microbial metabolites and microbial-associated molecular patterns reshape the tumor microenvironment by enhancing inflammation, promoting recruitment of myeloid-derived suppressor cells and tumor-associated macrophages, impairing cytotoxic T-cell function, and facilitating immune evasion and desmoplastic stromal remodeling. Conversely, selected microbial taxa may support antitumor immunity through immune activation and maintenance of tissue homeostasis. This figure was created with BioGDP.com. ECM, extracellular matrix; NK, natural killer; PanIN, pancreatic intraepithelial neoplasia; SCFA, short-chain fatty acid; TME, tumor microenvironment.

Adipokines regulate metabolic homeostasis, inflammatory cascades and immune surveillance through direct effects on the TME. Among these mediators, adiponectin is generally considered tumor-suppressive, whereas leptin promotes proliferative, angiogenic and pro-inflammatory signaling (98). The net effect of adipokine dysregulation in obesity therefore shifts the tumor ecology toward a PDAC-permissive state (98). These changes are reinforced by autophagy dysregulation, endoplasmic reticulum stress, oxidative stress, EMT and exosome secretion, all of which contribute to malignant transformation and tumor evolution (99-102). These observations support earlier pancreatic cancer screening in selected high-risk individuals, particularly those with new-onset diabetes or unexplained metabolic deterioration.

Obesity paradox in immunotherapy. The so-called obesity paradox has attracted growing interest in cancer immunotherapy. Although obesity is generally associated with an increased risk of PDAC and a chronic pro-inflammatory state (8), several clinical studies have reported comparable or, in some settings, improved responses to immune checkpoint inhibitors among obese patients (103,104). While the clinical relevance of this phenomenon remains incompletely understood, emerging evidence has suggested that obesity-associated alterations in the gut microbiome may interact with systemic and intratumoral immune pathways through multiple interconnected mechanisms. At the metabolic level, gut microbiota-derived SCFAs regulate colonic macrophage function and Treg cell homeostasis, while influencing host leptin secretion, a hormone that correlates with PD-1 expression on $CD8^+$ T cells and promotes pro-inflammatory macrophage polarization through TNF-α and IL-6 production (105). Immunologically, specific commensal bacteria such as *Bacteroides fragilis* modulate the balance between $CD4^+$ T cell subsets by mediating regulatory T cell conversion, whereas *Lactobacillus* species translocate to secondary lymphoid organs to influence Th1/Th17 responses (105). Notably, *Bifidobacterium* can stimulate antitumor immunity via T cell cross-reactivity between bacterial surface epitopes and tumor neoantigens (105). These microbiota-mediated immune

Table I. Emerging microbial- and vaccine-based therapies in PDAC.

Type	Therapy	NCT number	Phase	Status/results
Microbial therapy	FMT during colonoscopy and then FMT oral capsules	NCT04975217	Early phase I	Suspended
Personalized mRNA vaccine	Autogene cevumeran + atezolizumab + mFOLFIRINOX vs. mFOLFIRINOX alone	NCT05968326	Phase II	Recruiting
mKRAS peptide vaccine	ELI-002 2P	NCT04853017	Phase I	Completed; ~84% of patients developed mKRAS-specific T-cell responses; vaccine-induced immunity was associated with improved relapse-free survival and overall survival, and 67% of patients demonstrated antigen spreading
Personalized neoantigen vaccine	XH001 combined with immune checkpoint inhibition and chemotherapy	NCT06353646	Not applicable	Recruiting
Personalized mRNA vaccine	XP-004 plus PD-1 inhibitor	NCT06496373	Early phase I	Recruiting
Personalized mRNA vaccine	mRNA-0217/S001 with or without pembrolizumab	NCT05916261	Early phase I	Recruiting
Personalized mRNA vaccine	Personalized tumor vaccine combined with a PD-L1 inhibitor	NCT06156267	Early phase I	Not yet recruiting
KRAS-targeted mRNA vaccine	mRNA-5671/V941 with or without pembrolizumab	NCT03948763	Phase I	Terminated; no detailed PDAC-specific efficacy data have been reported publicly
Personalized mRNA vaccine	Personalized neoantigen mRNA vaccine	NCT03468244	Not applicable	Unknown status
PPV	PPV, alone or combined with imiquimod, pembrolizumab or sotigalimab	NCT02600949	Phase I	Recruiting

FMT, fecal microbiota transplantation; mFOLFIRINOX, modified FOLFIRINOX; PD-1, programmed cell death protein 1; PDAC, pancreatic ductal adenocarcinoma; PD-L1, programmed death-ligand 1; PPV, personalized peptide vaccine.

modulations collectively shape the tumor microenvironment, which is characterized in obese patients by increased infiltration of exhausted $CD8^+$ T cells with elevated PD-1 expression, enhanced natural killer cell activity and a pro-inflammatory M1-like macrophage phenotype, features that may underlie the improved therapeutic responses to immune checkpoint inhibitors observed in this patient population (105).

Evidence from diet-induced mice obesity models indicates that $CD8^+$ tumor-infiltrating lymphocytes exhibit impaired effector function, characterized by reduced expression levels of Ifng, Prf1 and Gzmb, together with a metabolic shift from glycolysis toward oxidative phosphorylation. Notably, this dysfunctional state is not accompanied by increased expression of canonical exhaustion markers (106). Diet-induced weight loss, but not semaglutide-induced pharmacological weight normalization, has been shown to restore T-cell effector function and improve responses to immunotherapy (106). These findings suggest that metabolic health, rather than body mass index alone, may influence antitumor immune competence and treatment efficacy. They are also consistent with the possibility that obesity-associated microbial and inflammatory states contribute to shaping immune fitness and drug responsiveness.

Although some studies have reported an association between obesity and improved survival in patients with pancreatic cancer, the obesity paradox in PDAC should currently be viewed as a hypothesis-generating concept rather than an established clinical paradigm (107). Several non-mutually exclusive mechanisms may contribute to the observed heterogeneity, including differences in body composition (visceral adiposity vs. sarcopenia), metabolically healthy

vs. unhealthy obesity phenotypes, treatment dose normalization and obesity-associated microbiome configurations that may influence immune priming (105,106). Future prospective studies incorporating metabolic, body-composition and microbiome-based stratification may help clarify causality, and facilitate the development of personalized immunotherapy strategies and microbiome-targeted co-interventions.

5. Conclusion

The emerging body of evidence positions the microbiome as an integral component of pancreatic cancer biology, orchestrating tumor initiation and progression through complex and interconnected mechanisms. Microbial communities across the oral-gut-pancreas axis actively contribute to carcinogenesis by inducing genotoxic stress, sustaining chronic inflammation and shaping the tumor immune microenvironment. During disease progression, distinct microbial taxa exert opposing effects; however, these influences converge on shared oncogenic pathways, including immune suppression, metabolic reprogramming and extracellular matrix remodeling. This conceptual framework highlights the microbiome as a dynamic and bidirectional regulator of pancreatic cancer rather than a passive ecological feature (Fig. 1).

The rapidly expanding landscape of microbiome-targeted, immune-modulatory and vaccine-based therapeutic strategies in PDAC is summarized in Table I, together with representative clinical-trial registration numbers (obtained from ClinicalTrials.gov). Increasing evidence suggests that the microbiome-immune axis may represent a therapeutically actionable component of the PDAC TME (23,108). Current investigational approaches encompass multiple complementary strategies, including microbiome modulation through fecal microbiota transplantation, probiotics, defined microbial consortia and dietary interventions (70); myeloid-targeted therapies aimed at disrupting CCL2-CCR2 signaling and MDSC recruitment (82,109); combination immunotherapy approaches designed to overcome T-cell exclusion and myeloid-dominant immune suppression (110); and therapeutic cancer vaccines intended to enhance tumor antigen presentation and T-cell priming (111,112). In parallel, emerging modalities such as oncolytic viruses, KRAS-targeted therapies combined with immune checkpoint blockade, and metabolic interventions in obese or diabetic patients are being explored for their potential to reshape antitumor immunity.

Among these approaches, personalized neoantigen vaccines have generated particular interest. Early clinical studies of autogene cevumeran have demonstrated durable neoantigen-specific $CD8^+$ T-cell responses and prolonged persistence of vaccine-induced T-cell clonotypes, supporting the feasibility of individualized immunotherapy in PDAC (112). Nevertheless, most microbiome-directed and immune-modulatory strategies remain in early-phase clinical development, and their long-term efficacy, optimal patient selection criteria and mechanisms of response require further investigation. Collectively, these ongoing studies highlight the growing translational potential of targeting the microbiome-immune axis and provide a framework for the development of more effective precision immunotherapy strategies in PDAC.

Notwithstanding these advances, critical gaps remain. The field is constrained by technical challenges in low-biomass microbiome analysis, limited ability to infer causality and insufficient understanding of temporal dynamics during tumor evolution. Moreover, the high degree of inter-individual variability and the influence of external factors complicate the identification of reproducible microbial signatures. The interactions between bacterial and fungal communities, as well as their collective impact on tumor biology, represent an additional layer of complexity that remains largely unexplored.

Future efforts should move toward a more integrative and translational paradigm. Comprehensive multi-omics profiling, coupled with longitudinal human cohorts and advanced experimental models, will be essential to dissect causal mechanisms and identify actionable targets. In parallel, the development of microbiome-based biomarkers for early detection and patient stratification, as well as therapeutic strategies aimed at reshaping microbial ecosystems, holds considerable promise. Ultimately, integrating microbiome science into precision oncology may redefine current approaches to pancreatic cancer, offering novel options to improve diagnosis, treatment and patient survival.

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YL and YF performed the literature review and wrote the manuscript. Data authentication is not applicable. Both authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools (ChatGPT; GPT-5.5; OpenAI; https://chatgpt.com) were used to improve the readability and language of the manuscript,

and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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