Mechanistic insights into pancreatic cancer progression from circadian rhythm disruption and gut microbiota dysbiosis (Review)

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Abstract. Pancreatic cancer has nearly doubled in incidence over the past two decades, becoming one of the deadliest types of malignancy in humans, with poor prognosis. With advances in modern medicine, the 5-year survival rate for pancreatic cancer has increased from <5% in 1990 to ~10% in 2021. Most patients are diagnosed at an advanced stage, and ~20% of patients diagnosed at an early stage are eligible for surgical resection, with a 5-year survival rate after surgery of up to 25%. With the aging population, the incidence of pancreatic cancer is expected to continue rising. The gut microbiota, a crucial ecosystem, comprises >1x10^{14} microorganisms that influence the development of pancreatic cancer through immune modulation and metabolites. Circadian rhythms, as a conserved molecular feedback loop, regulate cell metabolism and immune function, and their dysregulation is associated with metabolic disorders and tumor progression. Circadian rhythm disruption not only affects the gut microbiota and its metabolites but also accelerates pancreatic cancer progression through mechanisms such as promoting inflammation, immune suppression and drug resistance. The present review summarizes the impact of circadian rhythm dysregulation on the gut microbiota and its metabolites, specific microbiota associated with pancreatic cancer and their mechanisms in tumor progression and aims to deepen the understanding of the role of gut microbiota in pancreatic cancer treatment, providing a theoretical basis for future therapeutic strategies.

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1. Introduction

From 1990 to 2017, the incidence of pancreatic cancer has increased (age-standardized incidence rate, 5.0/100,000 person-years in 1990 to 5.7 in 2017), positioning it among the most lethal types of human malignancy, largely due to its poor prognosis (1). Although progress has been made in contemporary medical practices, the 5-year survival rate for this disease has improved marginally, rising from <5% in 1990 to ~10% by 2021 (2). This limited survival benefit is primarily associated with delayed detection, as a majority of patients are diagnosed at a later stage of the disease. In cases where early diagnosis is achieved, ~20% of individuals meet the criteria for surgical resection. For those who undergo surgery, the 5-year survival rate may increase to ~25% (3). As the risk of pancreatic cancer is associated with aging, the prevalence of the disease is projected to escalate in response to the global aging trend (4). Anatomically, the pancreas is connected to the gastrointestinal system via the pancreatic duct, which facilitates the retrograde movement of intestinal microorganisms into the pancreatic ductal system. This microbial translocation and resulting dysbiosis may contribute to sustained inflammatory responses, offering a potential explanation for the higher frequency of pancreatic ductal adenocarcinoma (PDAC) in the pancreatic head compared with its body or tail (5). The gut microbiota, a complex and essential component of the human organism, comprises >1x10^{14} microbial cells (6). Certain bacteria-associated metabolites, such as nitrosamines, may

modulate the immune landscape and influence resistance to treatment, thereby serving a role in the development and progression of pancreatic cancer (7).

The circadian clock is a conserved molecular feedback loop that regulates signaling pathways, controlling cell metabolism and immune function (8). Disruption of circadian rhythms leads to misalignment between external signals and the internal clock, resulting in metabolic dysregulation (9). A previous study has revealed circadian rhythm dysfunction in PDAC, which is associated with tumor progression and poor prognosis (10). Additionally, the gut microbiome exhibits circadian variations (11). For example, enteric Enterobacteriaceae in the gastrointestinal tract are sensitive to melatonin, a neurohormone secreted into the gastrointestinal lumen, and exhibit circadian patterns of aggregation and motility (12). Disruption of circadian rhythms alters the gut microbiota and its metabolites, thereby promoting cancer development (13). Therefore, circadian rhythm disturbances may contribute to the development of pancreatic cancer by affecting the gut microbiota and its metabolites. Previous reviews have primarily focused on the association between either circadian rhythms or the gut microbiota and pancreatic cancer (14,15). To the best of our knowledge, however, a comprehensive discussion linking circadian rhythm, gut microbiota and pancreatic cancer has been lacking. The present review aimed to summarize the impact of circadian rhythm disruption on the gut microbiota and its metabolites and discuss microbiota associated with pancreatic cancer, exploring how microbiota and metabolites influence pancreatic cancer progression. The aim of the present study is to enhance understanding and application of gut microbiota in the treatment of pancreatic cancer.

2. Methods

PubMed (pubmed.ncbi.nlm.nih.gov/) and Web of Science (clarivate.com/academia-government/scientific-and-academic-research/research-discovery-and-referencing/web-of-science/) databases were searched from inception to October 2025 for relevant literature, with the language restricted to English. The search strategy focused on the association between circadian rhythm, gut microbiota and pancreatic cancer. Key words included 'circadian rhythm', 'circadian disruption', 'gut microbiota', 'microbial metabolites', 'pancreatic cancer', 'pancreatic ductal adenocarcinoma', as well as mechanism-related terms such as 'LPS', 'SCFAs', 'immune suppression', and 'TLRs'.

The present study included original studies (including *in vitro* and *in vivo* experiments, animal studies, clinical observations and trials) that explored the association between pancreatic cancer, circadian rhythm disruption, gut microbiota and their metabolites, immune regulation, tumor microenvironment, gut-pancreas axis or microbiota-mediated drug resistance. In addition, high-quality review articles were used to supplement background information and theoretical frameworks.

Excluded studies included those not clearly involving the mechanisms of circadian rhythm or gut microbiota in non-pancreatic cancer research, non-English publications, conference abstracts, non-peer reviewed preprints, incomplete case reports and commentaries or editorials with low relevance to the review topic.

A total of two authors independently conducted the initial screening and full-text review of all retrieved articles. Disagreements were resolved through discussion, with arbitration by a third reviewer when necessary.

The present review did not conduct a meta-analysis due to substantial heterogeneity between the included studies in terms of study populations, exposure assessment and outcome definitions, as well as partial overlap among cohorts. Under such conditions, a quantitative synthesis may lead to inappropriate weighting or potential double-counting of results. The present study extracted and reported the effect sizes and corresponding uncertainty measures from the original publications, including odds ratio (OR), hazard ratios (HRs), standardized incidence ratios (SIRs), areas under the receiver operating characteristic curve (AUROCs), 95% confidence intervals (95% CI), as well as the study designs and population characteristics for each study.

3. Disruption of circadian rhythm and pancreatic cancer risk

Sleep disorders include conditions such as insomnia, narcolepsy and rapid eye movement sleep behavior disorder (16). Engaging in shift work, which requires activity during usual sleep periods, can disturb circadian rhythms (17). As reported by the International Agency for Research on Cancer in 2019, such circadian disruption is associated with elevated cancer risk (17). Gu *et al* (18) suggested that residents of the western regions of the United States, where there is a temporal discrepancy between natural sunlight exposure and internal biological clocks, may face an increased likelihood of circadian rhythm misalignment. This misalignment is a potential contributor to the development of diseases such as pancreatic cancer (18). In a study by Parent *et al* (19), data from 3,137 male patients with cancer patients were analyzed, revealing that those with a history of night shift employment exhibited a notably higher risk of pancreatic cancer (OR: 2.27, 95% CI: 1.24-4.15), although no significant association was observed between cancer risk and the total duration of night shift work. Moreover, findings from a Cox proportional hazards model based on 464,371 individuals indicate that those residing in areas with increased nighttime light exposure have a 27% greater risk of developing PDAC compared with individuals exposed to lower levels of night lighting (HR: 1.24, 95% CI: 1.03-1.49) (20). Additionally, Mendelian randomization analysis by Titova *et al* (21) demonstrated that a genetic tendency toward shorter sleep duration is associated with a heightened risk of pancreatic cancer (OR: 2.18, 95% CI: 1.32-3.62). In the US National Institutes of health-American association of retired persons diet and health study prospective cohort, nighttime light exposure assessed by satellite remote sensing was positively associated with PDAC incidence, with the with individuals in the highest exposure quartile having an increased risk of PDAC compared with those in the lowest quartile (HR 1.24, 95% CI 1.03-1.49; male, HR 1.21, 95% CI 0.96-1.53; female, HR 1.28, 95% CI 0.94-1.75), suggesting that environmental circadian disruption may promote PDAC development (20). A case-control study from Canada based on 3,137 male patients with cancer showed that those who had ever worked night shifts had a notably increased risk of

pancreatic cancer (adjusted OR 2.27, 95% CI 1.24-4.15), and this association is not increased by longer cumulative duration of night shift work, suggesting that the exposure is more important than duration (19). Using a German health insurance database, a case-control study with propensity score matching included 37,161 gastrointestinal cancer cases and an equal number of controls; having a recorded sleep disorder in the year before diagnosis was associated with an increased overall odds of gastrointestinal cancer (OR 1.20, 95% CI 1.08-1.34), and site-specific analyses suggested higher odds for pancreatic cancer in the year preceding diagnosis, supporting a short-term association between sleep disorders and cancer that may reflect bidirectional interactions between circadian disruption and early tumorigenesis (22). An ecological analysis using longitude position within a time zone as a proxy for social jetlag covered 607 counties across 11 US states and showed that moving from the eastern to the western edge of the same time zone was associated with higher age-standardized incidence rates for overall malignancy and several site-specific cancers (risk gradients evaluated/5 degrees of longitude and remaining significant after multiple-comparison adjustments); although a distinct estimate for pancreatic cancer was not significant, this general pattern supports incorporating circadian disruption into etiological frameworks for pancreatic cancer (18). By contrast with the aforementioned positive signals, a meta-analysis pooling data from >8.4 million individuals across prospective and case-control studies found no significant increase in overall pancreatic cancer risk when comparing ever vs. never night shift work (pooled OR 1.007, 95% CI 0.910-1.104; pancreatic cancer k=6; heterogeneity I^2 3.2%), suggesting that discrepancies between studies may reflect differences in exposure metrics, occupational composition and confounding control, highlighting the need for more objective circadian measures to identify high-risk groups (23). Mendelian randomization analysis indicates that genetic predisposition to short sleep is associated with higher pancreatic cancer risk (OR 2.18, 95% CI 1.32-3.62), whereas genetic predisposition to long sleep is associated with lower risk (OR 0.44, 95% CI 0.25-0.79), but these associations are not significant after multiple testing correction and not replicated in external two-sample analyses, implying that the causal role of sleep duration in PDAC requires larger samples and stronger instruments for confirmation (21).

In sum, epidemiological signals linking circadian disruption to pancreatic cancer are modest and heterogeneous. Across cohorts, satellite-derived light at night shows small excess risks (highest vs. lowest exposure HR, 1.2-1.3), single case-control estimates for ever night shift work can be larger (OR ~2.3), whereas meta-analytic pooling under mixed exposure definitions demonstrate a pooled OR close to 1.0, indicating no clear overall association. Mendelian randomization analysis (21) using genetic variants as proxies for short sleep suggest risk but does not withstand multiple-testing and lacks replication. Heterogeneity may reflect exposure misclassification, occupational mix and incomplete control of smoking, adiposity and diabetes, and short-term elevations in sleep disorder diagnoses before cancer raise the possibility of reverse causation. Clinically, these data support pragmatic mitigation of circadian misalignment and incorporation of objective circadian metrics into risk stratification, using study designs that account for the induction and latency period between exposure and cancer diagnosis to clarify timing; peri-therapeutically, actigraphy-guided light and sleep alignment may be piloted alongside standard care to test whether circadian calibration improves treatment tolerance and clinical outcomes.

4. Circadian regulation of gut barrier microbiota and immunity in pancreatic cancer

The circadian clock is a multilayered temporal control system that synchronizes daily oscillations of the gastrointestinal barrier, immune response and metabolic pathways (24). Multiple studies indicate that disruption of host circadian rhythms reshapes both the composition and rhythmicity of the gut microbiota, alters systemic exposure to key microbial metabolites such as lipopolysaccharide (LPS) and short chain fatty acids (SCFAs), promotes chronic inflammation and immune imbalance within the tumor microenvironment and influences pancreatic cancer phenotypes (24,25). Conversely, selected microbial metabolites (such as SCFAs, acetate, propionate and butyrate) modulate core clock machinery in the host, which implies a bidirectional loop (26).

Host clock disruption reshapes microbiota and compromises the barrier in pancreatic cancer. Circadian rhythm disturbances may influence pancreatic cancer through alterations in the gut microbiome (Fig. 1). In mice, deletion of the core clock gene BMAL1 abolishes the diurnal oscillation of the phylum Bacteroidetes and decreases its absolute abundance relative to controls, indicating that host clock genes directly shape microbial rhythmicity and abundance structure (24). On a broader scale, the gut microbiota as a whole exhibits marked daily oscillations. Disrupted feeding rhythms and experimental jet lag disturb these oscillations and produce transferable metabolic imbalance, demonstrating that behavioral and environmental cues act through the microbiota to influence host metabolic outcomes (25). Evidence linking the upper gastrointestinal microbiome with pancreatic cancer comes from study of duodenal fluid and bile (22). In a prospective cohort, patients with PDAC who have shorter survival show enrichment of oral and opportunistic taxa in duodenal fluid, especially members of Fusobacteria and the genus *Rothia*, suggesting that upstream dysbiosis is associated with poor prognosis (22). Patients with severe obstructive sleep apnea have significantly higher fecal Fusobacterium levels and its abundance is positively associated with the apnea hypopnea index (AHI) (27). This suggests that sleep fragmentation and intermittent hypoxia selectively enrich proinflammatory taxa, a feature that may be shared with the unfavorable pancreatic tumor microenvironment (in linear regression, AHI is positively associated with the relative abundance of *Fusobacterium*, β=0.538) (27).

Circadian imbalance also directly impairs the intestinal epithelial barrier. Both genetic clock disruption and environmental light and dark phase misalignment increase epithelial permeability, facilitate endotoxin translocation and trigger systemic inflammatory responses, thereby creating an anatomical route for gut-derived molecules to enter the circulation (28). Classical sleep deprivation model further shows that progressively sleep restricted rats develop cultivable bacteria

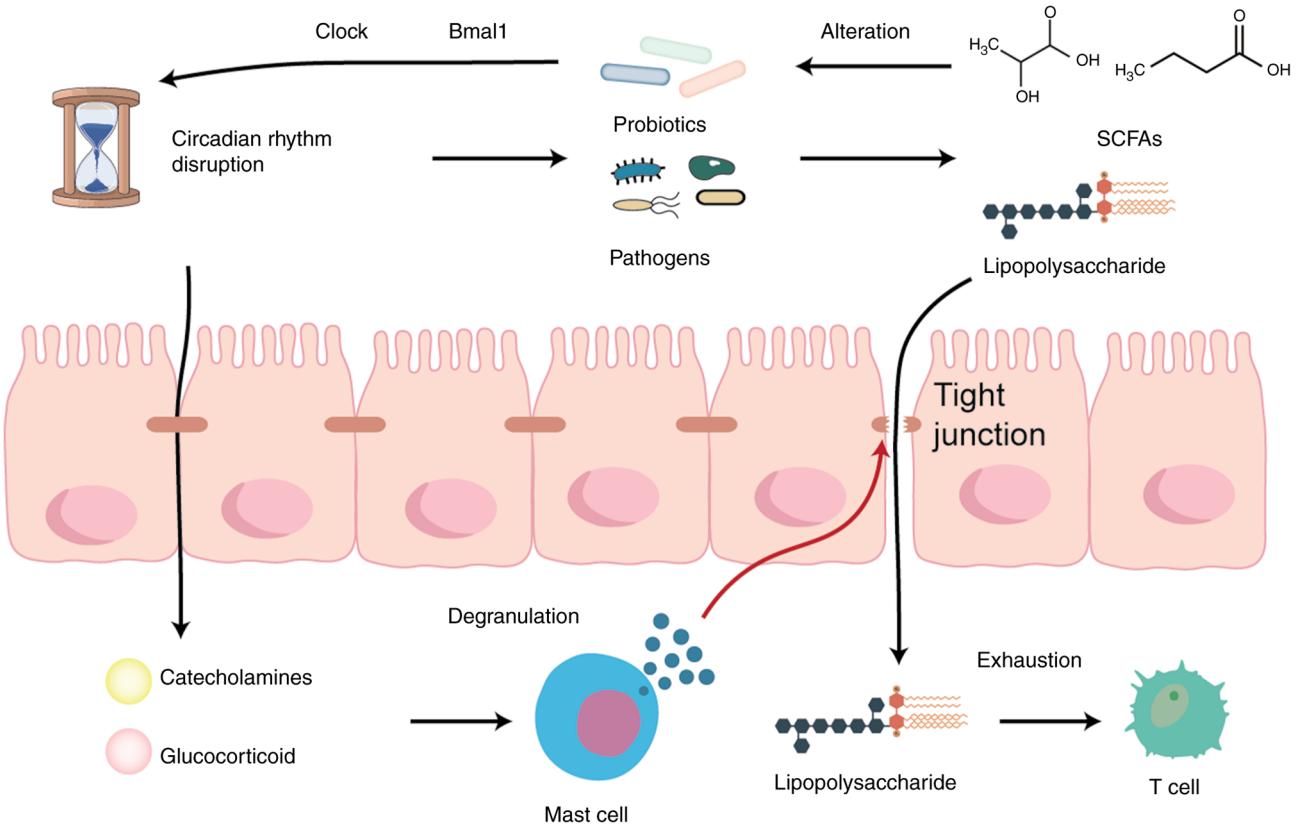

Figure 1. Circadian rhythm and gut microbiota. Disruption of the circadian rhythm not only leads to increased metabolites such as catecholamines and glucocorticoids, which trigger mast cell degranulation and damage the intestinal barrier, but also induces alterations in the gut microbiota. This results in the accumulation of harmful metabolites such as lipopolysaccharide, which can translocate through the intestinal barrier into the systemic circulation, leading to T cell exhaustion. Changes in gut microbiota-induced metabolites modulate the expression of host genes, such as Clock and Bmal1, further disrupting circadian rhythms. Figure created using Adobe Illustrator 2025 (Adobe, Inc.). Bmal1, brain and muscle ARNT-like 1; SCFA, short-chain fatty acid.

in tissue that is normally sterile, which supports translocation of microbes and their components across compromised barriers (29). Human study demonstrates that partial nocturnal sleep loss raises circulating norepinephrine and epinephrine levels, reflecting heightened sympathetic activity that is associated with inflammatory susceptibility (30). At the mucosal level, mast cell tryptase activates epithelial protease-activated receptor 2 to increase paracellular permeability, providing a cellular basis for stress-induced tight junction disruption and barrier leak (31). These barrier and inflammatory alterations align with pancreatic tumor biology. In a mouse model of PDAC, increased gut permeability elevates LPS levels in both the circulation and tumor tissue. The rise in LPS coincides with T cell infiltration while simultaneously inducing T cell exhaustion and loss of effector function, together establishing an immunosuppressive tumor microenvironment ($P<0.05$) (32).

Bidirectional coupling of microbial metabolites and the host clock in pancreatic cancer. Circadian disruption due to sleep disorders alters the microbial metabolic profile. Patients with severe obstructive sleep apnea show notably higher plasma D lactate levels, along with enrichment of proinflammatory gut taxa, suggesting that microbially derived lactate stereoisomers may serve as surrogate indicators of systemic metabolic stress (27). In mice, fecal microbiota transplantation from sleep deprived donors to healthy recipients reproduces colonic dysbiosis characterized by increased *Aeromonas* and endotoxins in serum and colon, and reduced butyrate levels, which indicates that circadian disruption drives inflammatory phenotypes through transferable microbe and metabolite consortia (33). In the aforementioned transplantation model, melatonin supplementation reverses dysbiosis, restores canonical butyrate producers including the Ruminococcaceae NK4A136 (an uncultured Ruminococcaceae clade) group, the Eubacterium xylanophilum group, Ruminococcus 1 and Ruminococcaceae A2, and alleviates inflammation. These findings imply that circadian signals improve host inflammatory status by rebuilding butyrate-producing niches (33). Functionally, SCFAs, especially butyrate, regulate immune cell and tumor cell phenotypes through G protein-coupled receptors and histone deacetylase pathways. SCFAs serve as metabolic substrates and epigenetic regulators and show anti-inflammatory and antitumor potential in cancer (26).

LPS, a Gram-negative cell wall component, is a key metabolite-associated mediator that links microbial rhythm disruption to systemic inflammation (28). LPS traverses the injured intestinal barrier and activates mucosal and systemic immunity, driving chemotaxis, adhesion molecule expression and cytokine cascades that provide sustained stimuli for immune exhaustion and fibrosis in pancreatic tumors (32). Endotoxin exposure and host responses show clear diurnal features. In healthy volunteers, fever and neuroendocrine responses to low dose endotoxin depend on time of day, indicating that human systemic sensitivity to LPS varies across the

circadian cycle (34). At the cellular level, mRNA expression of several toll-like receptors (TLRs), including TLR4, oscillates in splenic adherent immune cells over the 24-h cycle. LPS given at different times of day elicits distinct cytokine profiles, indicating that innate immune recognition is under circadian clock control (35). Consistently, the macrophage clock modulates LPS-induced NF-κB signaling and cytokine production through BMAL1 and microRNA (miRNA or miR)-155, imparting temporal specificity to endotoxin responses (36). Barrier dysfunction caused by circadian disruption increases exposure to microbiota-derived LPS in the circulation (28,37). In a light shift model, microbial community structure and function are altered, with enrichment of pathways involved in LPS biosynthesis, which suggests rhythm disturbance may both increase endotoxin supply and modify host responsiveness (38). Taken together, these observations indicate that the circadian clock interfaces with gut-derived LPS signaling in the pancreatic cancer microenvironment through regulation of epithelial permeability and time selective responsiveness of innate TLR4 pathways. The coexistence of dysbiosis and circadian misalignment may intensify immunosuppression in PDAC and confer temporal sensitivity to immunotherapy strategies such as PD-1 and PD-L1 blockade (39,40).

Microbial metabolites feed back onto host clock genes. Dietary choline is converted by gut microbes to trimethylamine and oxidized in the liver to trimethylamine N-oxide (TMAO) (41). In endothelial cell models *in vitro*, TMAO upregulates circadian locomotor output cycles kaput (CLOCK) and brain and muscle ARNT-like 1 (BMAL1) and modulates cell proliferation rhythms by coupling with long non-coding RNA and MAPK pathways, which suggests that certain metabolites remodel peripheral clocks (41,42). In summary, circadian disruption shapes a pancreatic tumor microenvironment in which proinflammatory immunity coexists with immune exhaustion through alteration of butyrate-producing niches and increased endotoxin exposure. Metabolites such as butyrate and TMAO influence host clock gene networks through receptor-mediated and epigenetic pathways. This bidirectional coupling provides tractable entry points for mechanistic studies and intervention strategies (26,41).

Evidence across genetic, behavioral and clinical models supports a coherent chain from host clock disruption to dysbiosis, barrier leak and time-dependent immune dysfunction in pancreatic cancer. Loss of microbial rhythmicity following BMAL1 deletion (24) coincides with community shifts in humans, including enrichment of oral taxa in proximal gut among short-survival PDAC cases with measurable α-diversity decrease and β-diversity separation (22). Sleep fragmentation and intermittent hypoxia show a proinflammatory effect on fecal communities, exemplified by a positive association between AHI and Fusobacterium abundance in regression analyses (β=0.538) (27). Independent lines of evidence indicate barrier compromise and systemic activation, with partial sleep loss elevating catecholamine levels (30) and PDAC models linking increased permeability with higher circulating and intratumoral LPS alongside T cell infiltration with functional exhaustion (32). Metabolite-clock crosstalk is bidirectional, as butyrate depletion and enrichment of LPS pathway are associated with circadian misalignment (38), while TMAO upregulates CLOCK and BMAL1 *in vitro* (41), and melatonin restores canonical butyrate producers following dysbiosis transfer (33). These observations support clinical frameworks that integrate objective circadian phenotyping with multi-site microbiome and metabolite readouts, and pilot peri-therapeutic ecological calibration and time-informed immunotherapy scheduling to test translatability (40).

5. Gut microbiota and pancreatic cancer

The gut microbiota is a complex and finely balanced ecosystem, constituting the largest microbial community in the human body. It serves essential roles in protecting the host from infection, aiding digestion and regulating the immune system (43). Dysbiosis, or imbalance in the gut microbiota, is associated with a number of diseases, particularly metabolic disorders, including obesity, type 2 diabetes, non-alcoholic fatty liver disease and metabolic syndrome. Gut microbiota can reach the pancreas through the circulatory system and pancreatic ducts, suggesting a potential involvement in pancreatic pathophysiology (44). Antibiotic-mediated depletion of gut microbiota in mice increases the number of anti-tumor T cells [such as T helper (Th)1 and type 1 cytotoxic T cells], reduce pro-tumor cell populations (such as IL-17A and IL-10-producing T cells) and enhance the infiltration of effector T cells into pancreatic tumors, thereby boosting the immune system capacity to combat pancreatic cancer (45). These findings highlight the role of gut microbiota in modulating pancreatic cancer development through immune regulation, though the exact mechanisms remain to be elucidated.

Role of gut microbiota in pancreatic cancer development

Heliobacter pylori. Meta-analysis has demonstrated a notable association between serum positivity for *H. pylori* and an increased risk of pancreatic cancer, although no significant association was identified specifically for positivity with the cytotoxin-associated gene A (CagA) strain (pooled adjusted OR, 1.38, 95% CI 1.08-1.75) (46). These findings indicate that the effect of *H. pylori* infection on pancreatic cancer risk may depend on bacterial strain variation. Schulte *et al* (47) showed that individuals infected with $CagA^-$ *H. pylori* strains exhibit a notably elevated risk of developing pancreatic cancer (OR 1.30; 95% CI 1.02-1.65), whereas those with $CagA^+$ strains exhibit a reduced risk (OR 0.78; 95% CI 0.67-0.91). Consistent with these results, a meta-analysis involving 3,033 participants found a significant yet modest association between *H. pylori* infection and pancreatic cancer incidence. However, the aforementioned analysis did not reveal a significant association between the presence of $CagA^+$ strains and the occurrence of pancreatic cancer (overall pooled OR 1.47, 95% CI 1.22-1.77), and this association persisted when the analysis was restricted to the studies of higher methodological quality, defined as those scoring ≥6 on the Newcastle-Ottawa scale (high-quality subset OR 1.28, 95% CI 1.01-1.63). By contrast, the subgroup analysis limited to $CagA^+$ strains did not show a significant association with pancreatic cancer (OR 1.42, 95% CI 0.79-2.57) (48). The aforementioned studies suggest that the risk of pancreatic cancer may vary depending on the specific strain of *H. pylori*, although further investigation is needed to define the relationship (47). Beyond *H. pylori* strains, the ABO genotype may also play a role in this process. ABO blood

group antigens are expressed in the gastrointestinal epithelium and influence *H. pylori* adhesion, thereby regulating gastric and pancreatic secretion functions, which may impact pancreatic carcinogenesis related to dietary and smoking-associated nitrosamine exposure, thus influencing pancreatic cancer risk (49). *H. pylori* damages the gastric mucosa, leading to the formation of gastric ulcers. Gastric ulcers are typically associated with hypochlorhydria, creating an environment conducive to the accumulation of nitrites (50), which are carcinogenic and increase the risk of pancreatic cancer (51). This may explain why patients with untreated gastric ulcer face a heightened risk of pancreatic cancer. During years 3-38 of follow-up after ulcer diagnosis, the SIR was 1.20 (95% CI 1.10-1.40); at 15 years of follow-up, the SIR was 1.50 (95% CI 1.10-2.10); and 20 years after gastric resection, the SIR was 2.10 (95% CI 1.40-3.10) (52). Alcohol consumption may also play a role in *H. pylori*-induced pancreatic cancer, as infection with *H. pylori* may increase pancreatic cancer risk in low-alcohol consumers (overall adjusted OR 1.25, 95% CI 0.75-2.09; never smokers-adjusted OR 3.81, 95% CI 1.06-13.63; low-alcohol consumers-adjusted OR 2.13, 95% CI 0.97-4.69) (53).

Fusobacterium. A cohort study detected *Fusobacterium* DNA in pancreatic cancer tissue and linked its presence to poor prognosis; patients with *Fusobacterium*-positive tumors show significantly shorter survival, supporting its potential as an adverse prognostic biomarker (multivariable HR for overall mortality 2.57, 95% CI 1.01-6.58; multivariable HR for cancer-specific mortality 2.16, 95% CI 1.02-4.59) (54). Mechanistically, mouse and human data indicate that intratumoral *Fusobacterium nucleatum* augments chemokine signaling and recruits granulocytes, thereby intensifying inflammatory conditions and promoting pancreatic cancer progression; activation of CXCL1 and its receptor CXCR2 is a key pathway (tumor tissue detection rate 15.5%) (55). Upstream sources may involve the upper gastrointestinal tract: Duodenal fluid analysis has shown that show enrichment of Fusobacteria and oral taxa such as Rothia in short-survival patients, suggesting oral-gut translocation and dysbiosis of the upper gut as a microbial reservoir for pancreatic colonization (discovery cohort n=308 with PDAC n=74; enrichment determined by differential abundance testing) (56). Intratumoral bacteria typically localize intracellularly within immune and cancer cells, a distribution that may facilitate immune evasion and direct crosstalk with host signaling networks (57). The pancreatic cancer microbiome induces suppression of innate and adaptive immunity, including polarization of tumor-associated macrophages toward immunosuppressive states and inhibition of T cell activation, thereby creating a niche favorable for pro-inflammatory colonizers such as *Fusobacterium* (antibiotic-mediated microbial depletion significantly decreases orthotopic tumor growth and myeloid suppressor populations and increases $CD4^+/CD8^+$ T cell infiltration) (58). The detection rate of *F. nucleatum* in pancreatic cancer is associated with prognosis and immune escape, further supporting its feasibility as an intervention target (59).

Veillonella and Streptococcus. A multi-center fecal metagenomic study developed specific pancreatic cancer classification models in which oral-associated genera including *Veillonella* and *Streptococcus* repeatedly emerge as discriminative features and retain stable performance in independent validation, underscoring their key roles in disease-associated communities (fecal metagenomic classifier AUROC up to 0.84; combination with CA19-9 increases AUROC to 0.94; external disease-specificity tested in 25 datasets at 90% specificity with low false-positive rates) (60). An independent Israeli amplicon-based study similarly reported increased relative abundance of *Veillonellaceae* and *Akkermansia* in feces from patients with pancreatic cancer, along with depletion of families common in healthy controls such as *Clostridiaceae*, *Lachnospiraceae* and *Ruminococcaceae*, and achieved an AUC of 82.5% for distinguishing patients with pancreatic cancer from healthy controls (61). A prospective Chinese fecal study further showed decreased overall α diversity and enrichment of inflammation-related functions such as LPS biosynthesis, and highlighted associations between *Streptococcus* and intestinal bile factors, suggesting potential interactions between altered bile dynamics and expansion of oral taxa (62). Multi-site sampling combined with fluorescence *in situ* hybridization (FISH) confirms that characteristic oral-gut taxa can be detected in pancreatic tumor tissue *in situ*, strengthening the biological continuity between oral-gut sources and pancreatic colonization (60).

Akkermansia muciniphila and butyrate-associated commensal organisms. Metagenomic analysis of long-term survivors has revealed enrichment of commensal organisms associated with antitumor immunity, most notably *Faecalibacterium prausnitzii* and *A. muciniphila*, relative to typical pancreatic cancer cases; both taxa are associated with favorable responses to immunotherapy in other types of malignancy, suggesting they may modulate pancreatic cancer progression by promoting antitumor immunity (significant enrichment of *F. prausnitzii* and *A. muciniphila* reported with metagenomic testing) (63). A cross-cohort stool and tissue study identified Akkermansia as a recurrent feature in diagnostic models, with in-tumor validation by FISH, consistent with potential migration from the gut and niche adaptation within the pancreas (fecal AUROC up to 0.84, rising to 0.94 with CA19-9) (60). Concordant with Israeli amplicon data, pancreatic cancer cohorts frequently show higher levels of Akkermansia and Veillonellaceae alongside decreased levels of Ruminococcaceae and other butyrate-associated families, a directional shift aligned with perturbations in mucosal barrier integrity, SCFA homeostasis and immune regulation (AUC 82.5% for a taxa-based classifier) (61). At the tissue level, the intratumoral microbiome is coupled with the host immune landscape; tumors from long-term survivors harbor more diverse microbial networks that are associated with features of T cell activation, including increased intratumoral $CD3^+$ and $CD8^+$ T cell infiltration and higher numbers of granzyme B-positive cytotoxic T cells, providing histological support for the hypothesis that butyrate-associated commensal organisms shape antitumor immunity via metabolic and antigen-presentation pathways (64). Systemically, immunosuppression driven by the pancreatic cancer microbiome is partially reversed by microbiota depletion, in line with the enrichment of beneficial commensal organisms in long-term survivors and supporting microbiome-based strategies to improve antitumor immune

responses (antibiotics decrease tumor burden and reprogram myeloid/T cell compartments) (58).

Porphyromonas gingivalis and oral-gut translocation. Oral pathobionts are associated with pancreatic cancer (60,65). Mechanistically, *P. gingivalis* can colonize pancreatic tumors and accelerate the growth of orthotopic and ectopic pancreatic cancer by inducing tumor-associated neutrophils to secrete neutrophil elastase, thereby establishing a neutrophil-dominated pro-inflammatory microenvironment (65). Detection of this oral pathogen in both tumor tissue and the oral cavity reinforces the anatomical route for oral-gut translocation and distal colonization, and implies that periodontal disease control may have practical relevance for pancreatic cancer prevention and peri-therapeutic management (65). Elevated intratumoral microbial loads coexisting with immune suppression may provide a niche that permits the persistence of oral taxa, consistent with findings that microbial depletion activates anti-tumor immunity and restrains tumor growth (58). Moreover, multi-site sequencing and ISH confirm that characteristic gut and oral bacteria can be directly visualized within pancreatic tissue, providing anatomical evidence for the involvement of oral microbes in pancreatic cancer progression (fecal classifier AUROC up to 0.84 with tissue-level FISH validation in a subset) (60).

Microbial communities within the pancreas. In the context of pancreatic cystic lesions, intraductal papillary mucinous neoplasm (IPMN) is reported as a potential precursor to invasive pancreatic cancer (66). Notably, in patients with IPMN with high-grade dysplasia and cancer, bacterial 16S rDNA copy numbers and IL-1β protein levels in cystic fluid are significantly higher compared with patients with non-IPMN pancreatic cystic neoplasm (16S rDNA geometric mean 17.7-fold higher in IPMN with high-grade dysplasia vs. IPMN with low-grade dysplasia; IL-1β 103.2-fold higher) (66). This suggests that an increase in intra-pancreatic bacteria may be associated with pancreatic cancer pathogenesis. Riquelme *et al* (64)demonstrated that pancreatic tissue from long-term survival patients with PDAC exhibit notably higher α-diversity in their pancreatic microbiomes. Additionally, specific microbial taxa (Pseudoxanthomonas, Streptomyces, Saccharopolyspora and *Bacillus clauii*) within the tumor microbiome are significantly associated with prolonged survival (64). These findings indicate that not only do specific microbial communities exist within pancreatic cancer tissue, but they also exhibit distinct patterns depending on the disease state. The pancreatic duct and the intestine are anatomically connected, with interactions between the pancreas and the gut facilitated by the pancreatic duct. FISH with 16S rRNA probes and quantitative PCR results indicate that the bacterial population in the pancreas of patients with pancreatic cancer is 1,000 times higher than that in healthy pancreatic tissue (67). Certain bacteria migrate through the pancreatic duct and accumulate in pancreatic cancer tissue (67). In the adult gut microbiome, Bacteroidetes and *Firmicutes* are dominant, while *Actinobacteria*, *Proteobacteria* and *Verrucomicrobia* are present at lower levels (68). However, in the gut microbiota of patients with pancreatic cancer, the relative abundance of *Proteobacteria*, *Actinobacteria*, *Fusobacteria* and *Verrucomicrobia* is notably increased. Correspondingly, an abnormal increase in *Proteobacteria* is also detected in the pancreatic microbiota of these patients, with the abundance of *Proteobacteria* associated with pancreatic cancer progression (58). These findings suggest that the gut microbiota influences the abundance of microbial communities within the pancreas and may serve a role in the development of pancreatic cancer. Furthermore, the microbial communities within pancreatic cancer tissue selectively activate TLRs, triggering immune tolerance responses that contribute to immune evasion in pancreatic cancer (69). For examples, the abundance of *B. pseudolongum* in both pancreatic cancer tissue and the gut of patients with PDAC is increased. The cell-free extracts of *B. pseudolongum* selectively activate TLR2 and TLR5, promoting macrophage polarization and subsequent secretion of immune-suppressive cytokines, such as IL-10, which provide immune protection for the tumor (58). In addition, the presence of Gammaproteobacteria in pancreatic cancer tissue has been reported (70). These bacteria secrete enzymes, such as cytosine deaminase, which convert gemcitabine, a chemotherapeutic agent used for PDAC, into its inactive form, 2',2'-difluorodeoxyuridine (70). This results in the development of gemcitabine resistance in pancreatic tumors, which is reversed by ciprofloxacin treatment (70). Moreover, *H. pylori* DNA is detected in 75% of pancreatic tissue samples and 60% of duodenal samples from patients with exocrine pancreatic cancer. This suggests *H. pylori* may be transmitted from the digestive tract to the pancreas, potentially promoting the development of pancreatic cancer and chronic pancreatitis (71). *H. pylori* stimulates pancreatic cancer cells to secrete IL-8, VEGF, NF-κB, activator protein 1 and serum response element, which enhance immune responses, angiogenesis and promote cancer cell proliferation and survival (72). Additionally, *F. nucleatum*, a bacterium associated with periodontal disease, has been detected in pancreatic cancer tissue (prevalence, 8.8%) (54). Patients with Fusobacterium positivity have notably higher cancer-specific mortality rates, suggesting that the presence of Fusobacterium in pancreatic tissue is independently associated with poor prognosis in pancreatic cancer (54).

Collectively, oral-gut pathobionts expand along the oral/duodenal/pancreatic continuum and align with adverse phenotypes (56). Intratumoral Fusobacterium is associated with shorter survival after adjustment for clinical covariates, with HR of ~2 two, and tumor positivity is observed in a minority of cases, suggesting a high-risk microbial subset rather than a ubiquitous marker (54). *H. pylori* shows strain-contingent signals, with pooled ORs for seropositivity in the range of 1.3-1.5, a higher risk with CagA-negative strains near 1.30 and a lower risk with CagA-positive strains near 0.78 (47). Long-term gastric ulcer carries standardized incidence ratios between 1.2 and 2.1 across latency windows, consistent with nitrosation-associated pathways that may intersect with pancreatic carcinogenesis (52). Diagnostic modeling adds convergent support (60). Stool classifiers that elevate oral taxa such as *Veillonella* and *Streptococcus* have AUC values near 0.84 and approach 0.94 when combined with CA19-9, with external disease specificity maintained at high specificity thresholds (60), while an independent amplicon study reports an AUC near 0.825 (61). By contrast, commensal organisms linked to barrier integrity and immune tone, including

Akkermansia and butyrate-associated families, concentrate in long-survivor networks and track with T cell-active tissue states (64).

These findings suggest complementary avenues for translation. Biomarker development may use stool or tumor microbial signatures together with clinical markers such as CA19-9 to support risk stratification and prognostic assessment across settings (60). In parallel, peri-therapeutic ecological modulation can be tested through mechanism-guided hypotheses, including inhibition of the CXCL1 and CXCR2 chemokine axis to limit neutrophil recruitment (55), reprogramming of macrophages through TLR-based signaling (58) and mitigation of microbe-mediated drug metabolism (70). However, most available studies are associative and sensitive to sampling site and batch structure, and effect estimates vary with exposure definitions and host context. More persuasive mechanistic inferences require converging evidence that traces microbial sources to in-tumor localization, delineates immune consequences and demonstrates reversibility under intervention, accompanied by clear reporting of effect sizes and heterogeneity to clarify magnitude and generalizability.

6. Hepatitis viruses and pancreatic cancer

Patients with chronic liver disease associated with hepatitis B virus (HBV) and hepatitis C virus (HCV) commonly exhibit marked disturbances of the gut microbiota (73). Epidemiological evidence indicates that chronic HBV/HCV infection is associated with an increased risk of pancreatic cancer, positioning viral hepatitis as a key link between gut microbiota alterations and pancreatic cancer progression (74).

HBV and HCV, is a leading cause of death due to viral hepatitis (75). HBV and HCV are not only detected in the liver but also in extrahepatic tissue such as the pancreas (76). For example, Yoshimura *et al* (77) demonstrated hepatitis B surface antigen (HBsAg) positivity in the pancreatic tissue of patients with pancreatic lesions, and electron microscopy reveals structures resembling HBV core particles in both the nucleus and cytoplasm. Jin *et al* (78) demonstrated that HBsAg and HBcAg are expressed in both pancreatic cancer tissue (21%, 34/162) and non-tumorous pancreatic tissue (29%, 47/162) and that both HBsAg and HBcAg are significantly associated with the occurrence of chronic pancreatitis (78). The aforementioned study also revealed the presence of the S, C, and X genes of HBV in pancreatic cancer (20%, 6/30) and non-cancerous pancreatic tissue samples (26.9%, 7/26). Notably, HBV DNA and anti-HBc antibody positivity are significantly higher in patients with pancreatic cancer compared with healthy controls (78). Taranto *et al* (79) suggested that mild pancreatic injury, indicated by elevated pancreatic amylase levels, may occur during the early stages of acute viral hepatitis. Chronic HBV infection and the presence of HBsAg notably increase the risk of pancreatic cancer (80). Similarly, Iloeje *et al* (81) found that chronic HBV infection may be associated with an increased risk of pancreatic cancer, with a notably higher risk in HBsAg-positive patients with HBV DNA ≥300 copies/ml, compared with those with HBV DNA <300 copies/ml. Additionally, the rate of synchronous liver metastasis in HBsAg-positive patients and those with chronic HBV infection is significantly lower than in HBsAg-negative patients and non-HBV infection groups, suggesting that HBV infection may influence the occurrence of liver metastasis and serve as an independent prognostic factor in pancreatic cancer (82). Given the higher detectability of HBV DNA in patients with pancreatic cancer, this suggests a potential role of latent HBV infection in pancreatic cancer progression. Latent HBV infection may not only serve as a reservoir for HBV following HBsAg clearance but could also trigger a mild yet prolonged necrotic inflammatory process, promoting the development of pancreatic cancer (78). A meta-analysis has shown that HBsAg positivity is associated with an increased risk of pancreatic cancer, while anti-HBc positivity also suggests an elevated risk, though the findings are not statistically significant, indicating the need for further studies to clarify the association between chronic HBV infection and pancreatic cancer (83). Beyond HBV and HCV, torque teno virus (TTV), a liver-tropic virus first isolated from a patient with acute post-transfusion hepatitis in 1997, is considered a pathogenic factor in acute hepatitis (84). TTV has been detected not only in the liver but also in the pancreas: TTV DNA has been found in patients with unexplained hepatitis who later develop pancreatic cancer, suggesting a potential link between TTV and pancreatic cancer (85). However, further research is needed to confirm this association (85).

The role of hepatitis viruses in pancreatic cancer development may be associated with inflammation, as HBsAg and HBcAg positivity in pancreatic tissue significantly increases the incidence of chronic pancreatitis (78). Following liver transplantation, pancreatic inflammation occurs is often associated with acute HBV infection in the transplanted liver (86), supporting the hypothesis that HBV may induce pancreatic cancer through inflammatory mechanisms. Additionally, a previous study suggests a notable interaction between a history of diabetes and chronic HBV infection, further increasing the risk of PDAC (80). There is a higher incidence of latent HBV infection in diabetic patients compared with healthy controls, which may be linked to the high incidence of primary hepatocellular carcinoma in diabetic patients (87). The pathogenesis of type 2 diabetes also involves pancreatitis (88), supporting the potential role of HBV in promoting pancreatic cancer through inflammation. Moreover, hepatitis B virus X protein (HBx) expression upregulates ErbB4 and TGF-α expression, activating the PI3K/AKT, MAPK, and ERK signaling pathways, thereby promoting the proliferation and invasion of pancreatic cancer cells. Inhibition of the PI3K/AKT pathway reverses the effects of HBx in PDAC cell lines (89). Therefore, HBx may promote pancreatic cancer progression by modulating these pathways (89).

7. Mechanisms of gut microbiota-mediated pancreatic cancer progression

Microbial-induced inflammatory pathways. Pancreatic inflammation serves a key role in the development of pancreatic cancer, with evidence indicating a significantly higher risk of pancreatic cancer in patients with chronic pancreatitis (90). Increasing evidence suggests that microbial infection contributes to the progression of pancreatitis (91,92). Dysbiosis in the gastrointestinal microbiota leads to the proliferation of harmful bacteria, which disrupt the epithelial barrier,

allowing pathogenic bacteria to migrate to the pancreas. The colonization of these harmful bacteria in the pancreas triggers pancreatic inflammation (92). Serra *et al* (93) showed that Gram-negative bacteria contribute to the promotion of tumor-associated inflammatory responses.

The pro-inflammatory effects of microbes involve pattern recognition receptors (PRRs) and their associated signaling molecules. NOD-like receptors (NLRs), which are cytosolic PRRs, activate NF-κB signaling pathways upon recognition of microbial-associated molecular patterns (Fig. 2). This activation not only triggers NF-κB signaling but also promotes inflammasome formation (94). One of the key components of activated inflammasomes is caspase-1, which facilitates the cleavage and maturation of pro-inflammatory cytokines, such as IL-1β and IL-18 (95). Inflammasomes are key regulators of the host defense against pathogen invasion and maintaining intestinal microbial balance. Mice lacking NLRs exhibit alterations in gut microbiota and microbial dysbiosis, which leads to the development of inflammatory disease (96). Mice with NOD1, Nlrp3 or caspase-1 knockout show reduced acute pancreatitis induced by cerulein, indicating the key role of inflammasomes in the promotion of pancreatitis (97). Moreover, NOD1 responds to gut microbiota and promotes the activation of NF-κB and STAT3. Activation of these pathways enhances the production of monocyte chemoattractant protein-1 (MCP-1), which recruits C-C chemokine receptor type 2-posotive ($CCR2^+$) inflammatory cells to the pancreas, thereby initiating pancreatitis (98). STAT3 is a key participant in pancreatitis and is activated in cerulein-challenged mice. In wild-type mice, STAT3 activation is transient and returns to baseline as the pancreas recovers from cerulein-induced acute pancreatitis. However, in KC mice (mice with KRAS mutations in pancreatic epithelial cells), STAT3 activation persists due to the recruitment of myeloid cells, which secrete IL-6, activating STAT3 in the pancreas (99,100). Persistent STAT3 activation promotes the expression of cytokines, chemokines and other mediators, such as IL-6 and COX2, further driving pancreatic cancer progression (100,101). Additionally, STAT3 induces the expression of MMP-7, which facilitates tumor metastasis (99). Germ-free mice exhibit fewer gastrointestinal malignancies, potentially due to decreased tumor-associated inflammation (102). This anti-tumor effect was also confirmed in mice treated with antibiotics to decrease gastrointestinal microbiota (102). Although the aforementioned studies have not been verified in pancreatic cancer models, similar evidence suggests that antibiotic-induced gut sterilization alleviates acute pancreatitis (91).

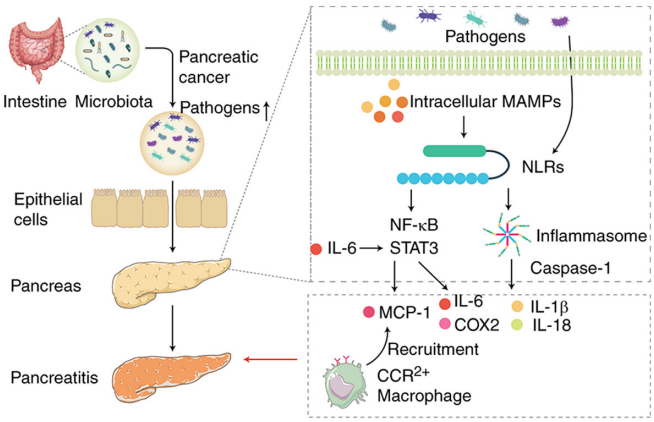

Figure 2. Microbial infection and inflammatory pathways in pancreatitis and cancer development. Dysbiosis of the gut microbiota leads to the proliferation of harmful bacteria, disrupting the intestinal epithelial barrier and allowing pathogenic bacteria to migrate to the pancreas, triggering an inflammatory response. NLRs activate the NF-κB signaling pathway and promote inflammasome formation following recognition of MAMPs. A key component of inflammasomes, caspase-1, facilitates the maturation of pro-inflammatory cytokines such as IL-1β and IL-18, exacerbating the inflammatory response. NOD1 responds to gut microbiota and activates the NF-κB and STAT3 pathways, leading to the production of MCP-1, which recruits $CCR2^+$ inflammatory cells to the pancreas. Persistent activation of STAT3 promotes the production of cytokines and chemokines such as IL-6 and COX2. Figure created using Adobe Illustrator 2025 (Adobe, Inc.). MAMP, microbial-associated molecular pattern; NLR, Nod-like receptor; MCP, monocyte chemoattractant protein-1; CCR, C-C chemokine receptor.

Gut microbiota regulation of the immune system in pancreatic cancer. Changes in the gut microbiota present within pancreatic cancer tissue contribute to immune suppression within the tumor microenvironment (Fig. 3). Pushalkar *et al* (58) demonstrated that administering oral antibiotics to eliminate gut microbiota effectively inhibits tumor progression. However, this effect is not observed in recombination activating gene 1 (Rag1) knockout mice, suggesting that the immune system is essential for gut microbiota-mediated regulation of tumor development (45). Furthermore, depletion of gut microbiota led to a marked increase in T cells producing IFN-γ, while the populations of T cells secreting IL-17A and IL-10 are notably decreased (45). In the pancreatic cancer tumor microenvironment, the Th2/Th1 ratio is considered an independent prognostic marker for patient survival. A decrease in this ratio is associated with notably prolonged overall survival (103). This suggests that the removal of gut microbiota inhibits tumor growth by increasing Th1 responses and decreasing Th17 and regulatory T cell responses. Thomas *et al* (104) investigated the effects of microbiota depletion in $Kras^{G12D}/PTEN^{lox/+}$ mice, showing that microbiota-depleted mice exhibit fewer poorly differentiated tumors. Furthermore, in a xenograft model of PDAC in non-obese diabetic/severe combined immunodeficiency (NOD-SCID) mice, tumor growth is inhibited in microbiota-depleted mice compared with microbiota-intact controls (104). The aforementioned study also observed a notable increase in $CD45^+$ immune cells within PDAC xenografts derived from mice subjected to gut microbiota depletion, implying intestinal microbiota may contribute to the suppression of innate immune responses (104). Pushalkar *et al* (58) demonstrated that in KC mice (Kras; $p48^{Cre}$), the decrease in gut microbiota resulted in diminished infiltration of myeloid-derived suppressor cells within tumor tissues. This microbial alteration also facilitates the polarization of tumor-associated macrophages toward the pro-inflammatory M1 phenotype and supports the differentiation of $CD4^+$ Th cells toward the Th1 subtype. Additionally, microbiota depletion leads to a significant rise in the expression of PD-1 on effector T cells (58). Fecal bacteria from PDAC mice inhibit the tumor-protective effects observed in microbiota-depleted KC mice, whereas fecal bacteria from normal mice do not have this effect (58). The immunosuppressive effects of PDAC-associated bacterial extracts are abolished in macrophages lacking TLR signaling (58). These observations

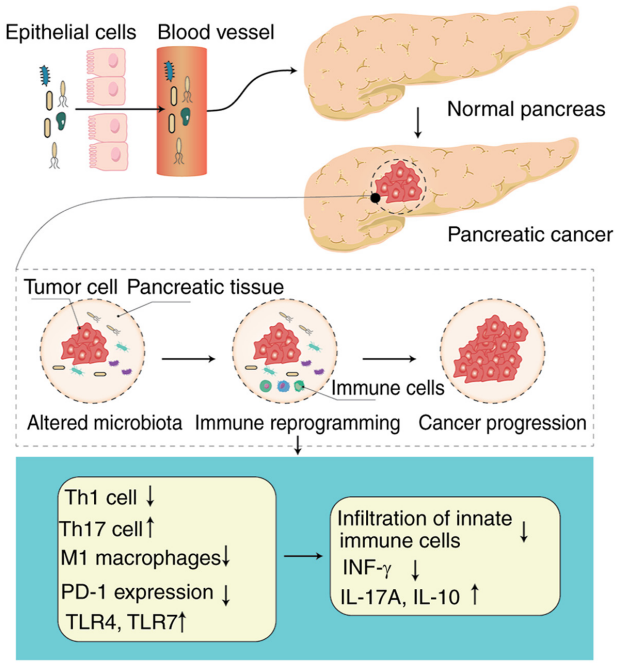

Figure 3. Gut microbiota and immune suppression in pancreatic cancer. Alterations in the gut microbiota within pancreatic cancer tissue lead to immune suppression in the tumor microenvironment. These microbiota changes result in a decrease in Th1 cells, an increase in Th17 cells, suppression of M1 macrophage polarization and decreased PD-1 receptor expression on T cells. The microbiota shift promotes the expression of TLR4 and TLR7 on cancer cells. These microbial changes also contribute to reduced immune cell infiltration and lower secretion of immune factors at the tumor site, which facilitates tumor progression. Figure created using Adobe Illustrator 2025 (Adobe, Inc.). Th, T helper; TLR, toll-like receptor.

indicate that manipulating the gut microbiota may affect the effectiveness of immune checkpoint inhibitor therapy and they offer strong evidence for the role of gut microbes in reprogramming immune responses through TLR signaling pathways. TLRs are well-studied PRRs that detect pathogen- and damage-associated molecular patterns (DAMPs). When TLR activation is not properly regulated, it may result in impairments in immune function (105). Following activation, TLRs recruit signaling molecules such as MyD88 or TIR-domain-containing adapter-inducing interferon-β (TRIF), further activating the NF-κB and MAPK pathways. In patients with pancreatic cancer and mouse models, the expression of TLR4 and TLR7 is upregulated (106,107). The upregulated TLRs bind to DAMPs, promoting immune cell release of inflammatory mediators, which alter the tumor microenvironment and promote pancreatic cancer progression (106). Blocking MyD88 can inhibit the immunosuppressive effects of fecal-derived extracts from KC mice, evidenced by the activation of $CD4^+$ T cells and the upregulation of immune mediators such as lymphocyte function-associated antigen 1 (LFA-1), CD44, TNF and IFN-γ (58,107). These data support the hypothesis that gut microbiota mediates immune suppression and promotes tumor proliferation via TLRs, particularly TLR2 and TLR5 pathways and downstream MyD88 signaling.

Regulation of pancreatic cancer by microbial metabolites

SCFAs and pancreatic cancer. Microbes are key regulators of metabolic processes and studies have shown that microbial metabolites can impact both gut and systemic homeostasis, thereby influencing tumorigenesis (62,108) (Fig. 4). Evidence has outlined the primary categories of microbial metabolites and their potential association with pancreatic cancer (Table I) (110-115,117-119,123). Among these metabolites, SCFAs are a key group generated by the fermentation of indigestible carbohydrates through gut microbial activity (109). These include lactate, acetate and butyrate. Data obtained through single-cell RNA sequencing have identified a negative association between lactate metabolism markers and anti-tumor immune responses, along with disruptions in immune cell infiltration patterns (109). By contrast, these markers have shown a positive association with signaling pathways that support tumor progression (109). Furthermore, the elimination of lactate dehydrogenase A (LDHA), a key enzyme governing lactate production in pancreatic cancer cells, enhances the activity of $CD8^+$ T cells involved in anti-tumor immunity and improves the overall effectiveness of immunotherapy (109). A similar study (110) suggested that increased LDHA expression in the tumor microenvironment of PDAC is a poor prognostic factor for patients with PDAC. In a mouse model of PDAC enriched with cancer-associated fibroblasts (CAFs), LDHA depletion inhibits tumor growth (110). The aforementioned study also found that lactate is taken up by CAFs via monocarboxylate transporter 1, promoting CAF proliferation. Additionally, lactate upregulates IL-6 expression in CAFs, which suppresses immune cell activity (110).

Lactate induces the production of α-ketoglutarate in mesenchymal stem cells (MSCs). This activates 10-11 translocation enzymes, resulting in decreased DNA methylation and increased hydroxymethylation, an epigenetic modification that promotes MSC differentiation into CAFs, contributing to the invasive behavior of PDAC (111). Butyrate enhance alkaline phosphatase activity and facilitates the transformation of CD18 into CD11 cells, which contributes to the differentiation of pancreatic cancer cell lines and suppression of PDAC cell proliferation and invasion (112). Moreover, a butyrate compound conjugated with hyaluronic acid induces cell cycle arrest at both the G0/G1 and G2/M phases. This compound also promotes the expression of pro-apoptotic proteins such as Bax and caspase-7, while concurrently reducing the levels of angiogenesis-associated factors including VEGF-A165 and VEGF-D, thereby inhibiting the proliferation of the MIA PaCa-2 pancreatic cancer cell line (113). In a study by Ren *et al* (62), gut microbiota profiles of patients with pancreatic cancer and healthy controls were compared using MiSeq sequencing. The results indicated a higher abundance of pathogenic and LPS-producing bacteria in patients with pancreatic cancer patients, whereas levels of beneficial microbes, including butyrate-producing species and probiotics, are diminished (62). These findings are in line with the research by Kanika *et al* (114), who reported that sodium butyrate, a histone deacetylase inhibitor, decreases pancreatic fibrosis and injury induced by L-arginine in Wistar rats. Additionally, an *in vitro* study (115) has shown that treating cytotoxic T lymphocytes and chimeric antigen receptor T cells with pentanoate and butyrate can enhance their anti-tumor functions against pancreatic cancer. This is achieved through inhibition of class I histone deacetylase activity and upregulation of effector molecules such as CD25, IFN-γ and TNF-α (115). The

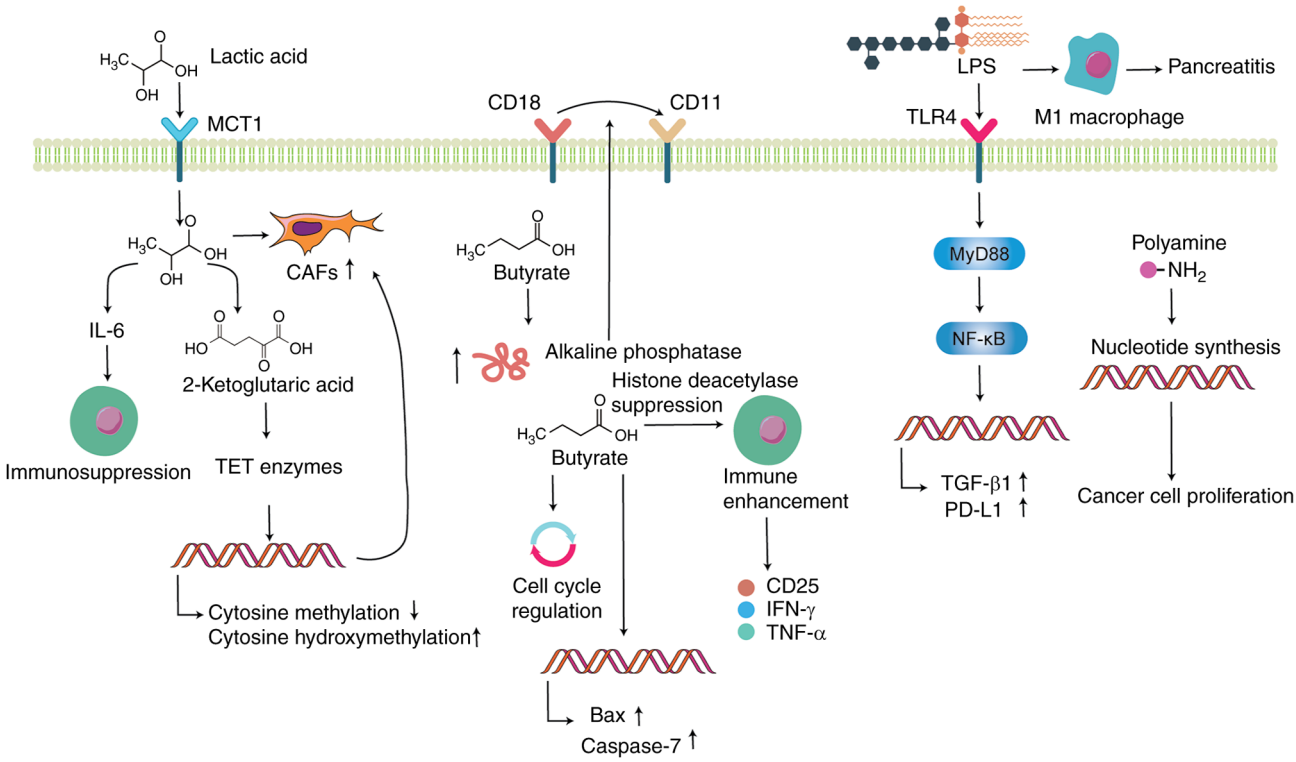

Figure 4. Gut microbiota metabolites and pancreatic cancer progression. Lactic acid, a short-chain fatty acid, is absorbed by CAFs via MCT1, promoting CAF proliferation and upregulating IL-6 expression, which suppresses immune cell activity and enhances CAF formation via α-ketoglutarate-dependent TET enzymes. Butyrate increases alkaline phosphatase activity, facilitating the conversion of CD18 to CD11 cells. Additionally, butyrate inhibits the cell cycle progression, increases the expression of pro-apoptotic proteins Bax and caspase-7 and suppresses pancreatic cancer cell proliferation. Butyrate enhances immune cell activity and stimulates the production of immune factors such as CD25, IFN-γ and TNF-α. LPS, via the TLR4/MyD88/NF-κB signaling pathway, elevates the production of PD-L1 and TGF-β1 in tumor cells, promoting pancreatic cancer progression. LPS promotes M1 polarization of macrophages, contributing to pancreatic inflammation. Polyamines drive tumor proliferation by promoting the synthesis of purine and pyrimidine nucleotides. Figure created using Adobe Illustrator 2025 (Adobe, Inc.). CAF, cancer-associated fibroblast; MCT, monocarboxylate transporter; TET, 10-11 translocation; LPS, lipopolysaccharide; TLR, toll-like receptor.

aforementioned studies suggest that different SCFA components may have distinct effects on pancreatic cancer. Future research should focus on modulating the gut microbiota, such as decreasing levels of lactate-producing microbes and increasing levels of butyrate-producing microbes, to regulate pancreatic cancer progression. However, further experimental studies are needed.

Role of LPS in pancreatic cancer. LPS, a notable component of the outer membrane of Gram-negative bacteria, is released into the surrounding environment under the action of antibiotics or host immune cells (116). In a co-culture system involving PDAC cells and macrophages (RAW 264.7), stimulation with LPS activates the NLRP3 inflammasome. This leads to elevated expression of pro-inflammatory cytokines IL-1β and TNF-α, which contribute to the formation of a pro-inflammatory tumor microenvironment and enhanced PDAC cell survival (117). Notably, this effect is mitigated by MCC950, a selective inhibitor of the NLRP3 inflammasome (117). Peng *et al* (118) established an acute pancreatitis model in C57BL/6J mice using cerulein combined with LPS. The results showed a marked increase in the expression of mixed lineage kinase domain-like protein (MLKL) and phosphorylated MLKL in pancreatic acinar cells, accompanied by a rise in M1-type macrophage polarization. Disruption of MLKL or neutralization of the chemokine CXCL10 decreases M1 macrophage polarization and alleviates the severity of acute pancreatitis in cerulein and LPS-induced acute pancreatitis C57BL/6J mice (118). Additionally, LPS has been shown to enhance the production of TGF-β1 via the TLR4/MyD88/NF-κB signaling pathway, thereby contributing to the pathogenesis of chronic pancreatitis (119). In PDAC tissue, LPS also upregulates PD-L1 expression through the same TLR4/MyD88/NF-κB pathway, facilitating tumor immune escape mechanisms (40). The aforementioned studies indicate that LPS promotes macrophage M1 polarization and contributes to the formation of an inflammatory pancreatic microenvironment, which accelerates the progression of pancreatic cancer, primarily via the NLRP3 inflammasome, MLKL/CXCL10 pathway and TLR4/MyD88/NF-κB signaling.

Polyamines in pancreatic cancer progression. Polyamines are small polycationic molecules that serve various biological roles, including gene regulation, stress resistance and cell proliferation and differentiation (120). Polyamines promote synthesis of purine and pyrimidine nucleotides by providing amino groups, which supports rapid cell proliferation, making them potential biomarkers for tumor progression (121). The gut microbiota is associated with polyamine concentrations and serves an essential role in regulating human gut polyamine levels (122). In PDAC mice, notable upregulation of the metabolic pathways associated with polyamine biosynthesis

Table I. Microbial metabolites and their associations with pancreatic cancer progression.

Authors, year	Metabolite	Model	Effect/mechanism	(Refs.)
Kitamura *et al*, 2023	Lactic acid	CAF-rich murine PDAC	CAFs take up lactate and promote their own proliferation via the TCA cycle; lactate stimulates CAFs to express IL-6 and inhibits the activity of cytotoxic immune cells	(110)
Bhagat *et al*, 2019		PDAC cells with CAFs	Lactate stimulates the production of α-KG in MSCs, activating TET enzyme, which decreases cytosine methylation and increases hydroxymethylation, promoting MSC differentiation into CAFs and boosting PDAC invasiveness	(111)
Mullins *et al,* 1991	Butyrate	HPAF cell line	Increased alkaline phosphatase activity notably promotes the transition of CD18 to CD11 cells, facilitates the differentiation of pancreatic cancer cell lines and inhibits the proliferation and invasion of PDAC cells	(112)
Pellizzaro *et al*, 2008		MIA PaCa-2 cells	Arrests the cell cycle at G0/G1 and G2/M phases, upregulates pro-apoptotic proteins Bax and caspase-7, downregulates angiogenesis-associated proteins VEGF-A165 and VEGF-D and inhibits proliferation of pancreatic cancer cells	(113)
Kanika *et al*, 2015	Sodium butyrate	Wistar rat	Inhibits L-arginine-induced pancreatic fibrosis and pancreatic injury	(114)
Luu *et al*, 2021	Valerate and butyrate	CTLs and CAR T cells	Inhibits the activity of class I histone deacetylase, enhances the anti-pancreatic cancer tumor activity of CTLs and CAR T cells, increases the expression of effector molecules such as CD25, IFN-γ and TNF-α	(115)
Sivam *et al*, 2023	Lipopolysaccharide	PDAC cells and RAW 264.7 macrophages	Promotes the activation of NLRP3 inflammasome, increases the expression of IL-1β and TNF-α, facilitates the formation of a pro-inflammatory microenvironment and enhances the survival of PDAC cells	(117)
Peng *et al,* 2023		C57BL/6J mouse	Promotes macrophage M1 polarization and exacerbates pancreatitis via the MLKL/CXCL10 pathway	(118)
Sun *et al*, 2018		Sprague-Dawley rat	Increases TGF-β1 production by activating the TLR4/MyD88/NF-κB signaling pathway, promoting the development of chronic pancreatitis	(119)
Mendez *et al*, 2020	Polyamine	KPC mouse	Metabolic pathways associated with polyamine biosynthesis are upregulated in the gut microbiota of PDAC mice and mice with PanIN show increased serum polyamine levels	(123)

α-KG, α-ketoglutarate; TET, 10-11 translocation; NLRP3, NLR family pyrin domain-containing 3; MLKL, mixed lineage kinase domain-like protein; CXCL10, C-X-C motif chemokine ligand 10; TLR4, toll-like receptor 4; MyD88, myeloid differentiation primary response protein 88; KPC, Kras/p53/Cre pancreatic cancer; PanIN, pancreatic intraepithelial neoplasia; PDAC, pancreatic ductal adenocarcinoma; CTL, cytotoxic T lymphocyte; CAR, chimeric antigen receptor; CAF, cancer-associated fibroblast; MSC, mesenchymal stem cell; TCA, tricarboxylic acid cycle.

in the gut microbiota is observed (123). Serum analysis shows increased polyamine concentrations in mice with pancreatic intraepithelial neoplasia, even without observable tumors (123). The aforementioned study also detected *Lactobacillus* in the gut

microbiota of 4-month-old LSL-Kras$^{G12D/+}$; LSL-Trp53$^{R172H/+}$; Pdx1-Cre) mice and metabolomic analysis demonstrates an association between *Lactobacillus* and polyamine metabolism (123). This confirms the role of polyamines as microbial metabolites in promoting pancreatic cancer progression. Similar finding has been reported in gastric cancer, where *H. pylori* regulates polyamine metabolism to facilitate tumor progression (124). The aforementioned studies suggest that gut microbiota imbalances, such as an increase in *Lactobacillus*, promote polyamine synthesis, thereby serving a notable role in pancreatic cancer progression. Future research should focus on the inhibition of polyamine metabolism and its association with pancreatic cancer to enhance microbiota modulation strategies for pancreatic cancer therapy.

Extracellular polymeric substance (EPS). In the clinical context of malignant biliary obstruction due to pancreatic cancer, intraductal drains and stents provide artificial surfaces that facilitate microbial adhesion and colonization (125). These conditions promote production of EPS and subsequent biofilm formation. EPS, which comprises polysaccharides, protein and extracellular DNA (eDNA), constitute the structural and functional core of biofilms (126). This matrix governs adhesion, antimicrobial tolerance, immune evasion and mechanical stability, thereby influencing the control of jaundice, the incidence of cholangitis and the timing and efficacy of systemic anticancer therapy (127,128). Before and after surgery, as well as during palliative treatment, >60% of pancreatic cancer cases arise in the pancreatic head, invade the bile duct and produce obstructive jaundice that necessitates endoscopic transpapillary stent placement (129). Multispecies communities and matrix-like EPS deposits emerge rapidly within the stent lumen. These changes form the pathological basis for stent re-occlusion and infection (129). Biliary stents retrieved from malignant obstruction associated with pancreatic cancer demonstrate that proteins and polysaccharides are the predominant, quantifiable components of the biofilm matrix. This implies a material basis linking EPS burden to stent failure (130). Metagenomic and culture-based investigation further shows that among patients undergoing pancreatic surgery or stent placement, biofilms within biliary stents are enriched with bacteria of oral and intestinal origin and contain gene clusters associated with biofilm formation and antimicrobial resistance (125). These findings indicate that diverse microorganisms in the biliary environment rely on EPS for adhesion, cooperative community behavior and drug tolerance (125). Consistent with these results, prospective cohort data show that plastic biliary stents are almost invariably colonized by bacterial and fungal biofilms with broad resistance spectra (131). This suggests that systemic antimicrobial therapy alone is unlikely to eradicate organisms embedded within biofilms, a limitation associated with the barrier function of EPS (131). With regard to clinical outcomes, in patients with gastrointestinal malignancy complicated by malignant biliary obstruction, the presence of cholangitis before percutaneous or endoscopic biliary drainage is associated with notably worse overall survival. This association indicates that biofilm-associated infection narrows the therapeutic window for systemic treatment in pancreatic cancer, with EPS-mediated barriers to both antimicrobials and host defenses as key etiological factors (132). Within EPS, polysaccharides and proteins crosslink through electrostatic and hydrophobic interactions to form a three-dimensional network. This network confers high viscoelasticity and low permeability, limits bacterial detachment under bile flow shear and restricts the diffusion of bile acids, antibiotics and complement. The resulting physicochemical shield provides the microscopic basis for biliary stent re-occlusion (133). eDNA, a key scaffold component of EPS, binds multivalent cations and cationic antimicrobial peptides, thereby depleting local divalent ions. This upregulates bacterial membrane modification pathways and increases the minimum inhibitory concentrations of aminoglycosides and cationic peptides by several-fold (134). This chemical antagonism has been demonstrated *in vitro* and may explain the persistence of biofilm-associated resistance in clinical settings (134). In a polymicrobial *in vitro* model, exogenous DNase alone or in combination with protease markedly weakens biofilm structure, decreases colony viability and improves antibiotic penetration (135). These findings suggest that enzymatic strategies targeting EPS degradation may serve as intrastent or locally irrigated adjuncts for infection associated with biliary stents in pancreatic cancer. Nevertheless, biliary safety and pharmacokinetics require clinical validation (136). Beyond common members of Enterobacteriaceae and enterococci, biliary stent biofilms may accumulate oral streptococci and actinomycetes (125). Features of the biofilm microbiota, such as polymicrobial community structure, dominance of taxa including *Streptococcus anginosus*, *Escherichia coli* and *Enterococcus faecalis*, and enrichment of biofilm and antimicrobial resistance genes, are associated with time to re-occlusion, which provides new evidence to support individualized stent management and materials science-based improvements in patients with pancreatic cancer (137).

Taken together, biliary obstruction resulting from pancreatic cancer and the use of drainage devices supply a stable substratum for microbial adhesion. EPS-driven biofilms exert system level effects on infection, re-occlusion, limit the access of host immune cells and soluble mediators to the stent surface and surrounding tissue, and alter drug permeability. These phenomena define a strategic bridge between device management in the biliary tract and the overall effectiveness of comprehensive therapy for pancreatic cancer.

Gut microbiota and chemotherapy resistance in pancreatic cancer. Surgical resection followed by adjuvant chemotherapy is the preferred treatment strategy for early-stage pancreatic cancer. However, drug resistance to chemotherapy notably contributes to poor clinical prognosis (138). Gemcitabine is the first-line chemotherapy drug for patients with pancreatic cancer not eligible for surgical resection (139). Evidence (70) has shown that certain bacteria, such as *Gammaproteobacteria* including *Escherichia coli*, in pancreatic tissue contribute to drug resistance by expressing long-form cytidine deaminase. This enzyme converts gemcitabine (2,2-difluorodeoxycytidine) into its inactive form (2,2-difluorodeoxyuridine), thereby leading to drug resistance (70). This finding is consistent with research by Bengala *et al* (140), which reported that high expression of cytidine deaminase (CDA) in patients with advanced pancreatic cancer is associated with significantly higher rates of early disease progression and shorter overall survival. In

addition, *Mycoplasma hyorhinis* infection is implicated in various types of cancer in humans, including gastric and colon carcinoma, esophageal and lung cancers, breast cancer and gliomas (141). Gemcitabine is converted into its inactive form in tumor cell extracts from *M. hyorhinis*-infected cells (142). Furthermore, the use of cytidine deaminase inhibitors restores the activity of gemcitabine in these cells, indicating that *M. hyorhinis* produces mycoplasma cytidine deaminase, which facilitates the metabolism of gemcitabine (142). Weniger *et al* (143) discovered that gemcitabine therapy improved progression-free survival in patients with pancreatic cancer negative for *Klebsiella pneumoniae*, but no significant improvement was observed in patients positive for this bacterium. Additionally, the use of quinolone antibiotics in *K. pneumoniae*-positive patients notably improved their overall survival. These findings suggest that *K. pneumoniae* may serve a key role in the development of gemcitabine resistance in pancreatic cancer (143). Moreover, in a type 2 diabetes mouse model, the development of hyperglycemia leads to significant changes in the gut microbiota, resulting in a poorer response of pancreatic cancer tumors to gemcitabine/paclitaxel treatment. Genomic analysis reveals that the microbiota in the diabetic group is enriched with bacteria involved in menadione biosynthesis (144). By increasing the concentration of menadione, these bacteria protect tumor cells from oxidative damage caused by chemotherapy, contributing to the development of drug resistance (144). *F. nucleatum* has been reported to promote pancreatic cancer progression (145). In colorectal cancer, *F. nucleatum* activates autophagy via the TLR4/MyD88 pathway and selectively inhibits certain miRNAs (such as miR-18a-3p and miR-4802), thereby leading to resistance to capecitabine (146). Udayasuryan *et al* (145) identified *Bacteroides ovatus* and *Bacteroides xylanisolvens* as positively associated with therapeutic efficacy. Oral administration of *B. ovatus* and *B. xylanisolvens* enhances the efficacy of erlotinib in a lung cancer mouse model (147). The aforementioned studies highlight that gut microbiota can influence the metabolism of chemotherapy drugs in the host and, through metabolic reprogramming, affect the efficacy of the drugs, leading to the development of drug resistance. This provides a direction for future research to improve chemotherapy efficacy by modulating specific gut microbiota.

8. Conclusion

The present review systematically explores how circadian rhythm disruption influences pancreatic cancer development by regulating the gut microbiota and its metabolites. With the increasing incidence of pancreatic cancer and its high mortality rate, there is need to gain a deeper understanding of its underlying pathological mechanisms to identify effective preventive and therapeutic strategies. Circadian rhythm disruption increases the risk of pancreatic cancer, with this heightened risk associated with changes in the gut microbiota. Disruption of circadian rhythms leads to an increased risk of *H. pylori* infection, which is associated with pancreatic cancer, and induces alterations in the abundance of microbiota associated with pancreatic cancer. This includes changes in the levels of microbial metabolites and disruption of the intestinal barrier, which allows pathogens, including LPS, to enter the systemic circulation. These pathogens and LPS promote the progression of pancreatitis, a risk factor for pancreatic cancer. Furthermore, gut microbiota also contributes to immune suppression in the host through TLRs. Metabolites from the microbiota, such as SCFAs, LPS and polyamines, regulate the progression of pancreatic cancer. Specific gut microbes are involved in the degradation of chemotherapy drugs, leading to the development of drug resistance. Integrating these findings, the present review proposes a coherent, bidirectional mechanistic framework: circadian disruption may promote the development of pancreatic cancer by reshaping the gut microbiota and its metabolites, while microbial metabolites such as butyrate and TMAO, in turn, regulate core clock components (CLOCK and BMAL1), potentially creating a feed-forward loop that reinforces circadian misalignment and tumor progression.

The gut microbiota is associated with risk factors for PDAC, such as diabetes, obesity and diet. Future research should focus on clarifying whether changes in the microbiota are primary initiators of cancer progression or responses to these factors. Future studies should investigate the dominant microbial communities in the gut and pancreatic tissue of patients with pancreatic cancer and analyze the relationship between gut and pancreatic microbiota. Such studies may facilitate the application of gut microbiota modulation in pancreatic cancer treatment. Additionally, considering the role of intra-pancreatic microbes in drug resistance, further research should explore the association between the dominant microbial communities in the pancreas and chemotherapy drug metabolism to improve the application of gut microbiota modulation in overcoming pancreatic cancer chemotherapy resistance.

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Authors' contributions

YaL and YoL performed the literature review and wrote the manuscript. HM, SD and CC constructed figures and tables. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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