

REVIEW ARTICLE

Prominent cellular metabolic adaptations in pancreatic ductal adenocarcinoma tumor microenvironment

Silin Xiang^{1,2†}, Shuai Sun^{2,3†*}, Pan Zhao^{2,4†}, Yanzhen Xu^{2,4,5}, Xu Mao^{2,4}, Xiaoying Tao^{2,4}, Junjun Du^{2,3}, Xiangyun He^{2,4}, Zhibo Zuo^{2,4}, Nan Li^{6*}, and Rongjing Zhou^{3*}

¹Graduate School, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China

²Pathology Residency Training Base, Hangzhou First People's Hospital, Westlake University, Hangzhou, Zhejiang, China

³Department of Pathology, Hangzhou Cancer Hospital, Hangzhou, Zhejiang, China

⁴Department of Pathology, Hangzhou First People's Hospital, Westlake University, Hangzhou, Zhejiang, China

⁵Department of Pathology, Hangzhou Geriatric Hospital, Hangzhou, Zhejiang, China

⁶Department of Pathology, The Second Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China

[†]These authors contributed equally to this work.

*Corresponding authors:

Shuai Sun
(sunshuai005@gmail.com);
Nan Li
(linanangel100@sina.com);
Rongjing Zhou
(zrjsh711@163.com)

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) represents a highly aggressive cancer with a dismal prognosis and a 5-year survival rate of approximately 12%. The poor clinical outcomes are attributed to multiple factors, including difficulty in early detection, rapid metastasis, and intrinsic resistance to therapies. The tumor microenvironment of PDAC exhibits immunosuppressive features, nutrient-deprived conditions, and metabolic reprogramming. These factors collectively contribute to immune evasion and therapeutic resistance. Notably, metabolic reprogramming has emerged as a well-recognized hallmark of PDAC in both cancer cells and the surrounding milieu. Several key metabolic pathways are extensively rewired to support tumor growth, survival, and progression. In addition, accumulating evidence highlights critical metabolic crosstalk between cancer cells and various components of the TME, including cancer-associated fibroblasts, tumor-associated macrophages, tumor-associated neutrophils, regulatory T cells, and the intratumoral microbiota. These metabolic interactions profoundly influence tumor biological behavior and therapeutic response. We aim to provide a comprehensive synopsis of recent advances regarding cellular metabolic adaptations in the PDAC tumor microenvironment, including glycolysis, glutamine and lipid metabolism, macropinocytosis, and autophagy. We delineate the multiscale metabolic interplays within the tumor–stroma symbiosis and highlight promising therapeutic strategies targeting metabolic vulnerabilities. We also discuss energy metabolism-associated post-translational modifications, such as lysine lactylation and acetylation. In this review, we focus on metabolic interactions among tumor cells, anti-tumor cells, and immunosuppressive cells, with an emphasis on recent technological advances, including single-cell sequencing, spatial multi-omics, and artificial intelligence.

Keywords: Pancreatic ductal adenocarcinoma; Tumor microenvironment; Drug resistance; Metabolic reprogramming; Chemotherapy

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a devastating malignancy with an extremely poor prognosis, exhibiting a 5-year survival rate of about 12%.¹ It is now the third leading cause of cancer-related mortality in the United States and is projected to rank second by 2040.² The poor prognosis is primarily attributed to late-stage diagnosis due to the absence of specific early symptoms, rapid and clinically silent metastasis, and profound resistance to therapy.³ Currently, fewer than 10% of PDAC cases are diagnosed at a stage amenable to curative resection, and 5-year survival rises greatly when the tumor is detected at stage I. This stark gap underscores the urgent and unmet need for early detection strategies. Recent advances in serum exosomal microRNA profiling, which have shown diagnostic value for identifying occult metastatic PDAC, also illustrate a methodological framework that could be extended to detect early-stage disease.⁴ While survival has modestly improved due to advances in supportive care, gemcitabine plus nab-paclitaxel and FOLFIRINOX (folinic acid, fluorouracil, irinotecan, and oxaliplatin) remain the mainstay of systemic treatment for advanced PDAC.⁵ Surgery is the only potentially curative option, yet only about 20% of patients are qualified for surgery at diagnosis, and recurrence is common.⁶

At the molecular level, Kirsten rat sarcoma viral proto-oncogene (*KRAS*), *TP53*, cyclin-dependent kinase inhibitor 2A (*CDKN2A*), and *SMAD4* are the most frequently mutated driver genes in PDAC. Indeed, somatic activating mutations in *KRAS* occur in more than 90% of cases and are also present in pancreatic intraepithelial neoplasia (PanIN) lesions.⁷ Codon 12 substitutions predominate in PDAC. *KRAS* G12D accounts for about 40% of cases, followed by G12V (about 30%) and G12R (about 15–20%). G12C and Q61 mutations are uncommon. Historically regarded as undruggable, *KRAS* is now emerging as an active therapeutic target, with promising inhibitors under clinical evaluation.⁸ In addition, germline *BRCA1/BRCA2* mutations define a subgroup of PDAC patients who may benefit from poly ADP-ribose polymerase inhibitors.⁹ Besides genetic susceptibility, other risk factors include smoking, high-fat diet, and chronic pancreatitis.^{10,11}

The PDAC tumor microenvironment (TME) is characterized by hypoxia, sparse vascularity, and elevated interstitial pressure, all of which impede drug delivery.¹² Immunotherapy, while transformative for many cancers, has largely failed in PDAC due to the immunosuppressive and exclusionary nature of its TME.¹³ Central to PDAC biology is metabolic reprogramming. It is also a well-recognized cancer hallmark.¹⁴ PDAC cells rewire multiple metabolic pathways, largely driven by oncogenic *KRAS*,

to sustain survival in this nutrient-poor milieu, and these adaptations are not confined to tumor cells but extend to the entire stromal cellular compartment^{15–17} (Figure 1). Previous reviews have examined PDAC metabolism from particular angles, such as tumor cell-intrinsic nutrient adaptation or glucose metabolism alone. But an integrated synthesis spanning the full cellular spectrum of the PDAC TME is still needed. Recent technological advances have substantially increased the resolution at which the TME can be interrogated, enabling more tractable characterization of individual cell populations. This in turn enriches our understanding of the microenvironment as an integrated whole. The present review seeks to provide a cross-compartment framework that systematically examines the metabolic interactions among tumor cells, cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), tumor-associated neutrophils (TANs), T lymphocytes, regulatory T cells (Tregs), and the intratumoral microbiota. We also incorporate recent developments from 2025 and 2026, including BHLHE40-driven TAN glycolysis, macrophage migration inhibitory factor-positive TAN subsets, zinc finger and BTB domain-containing protein 11 (ZBTB11)-mediated metabolic resistance to *KRAS* inhibitors, phosphoinositide kinase, FYVE-type zinc finger containing (PIKfyve)/*KRAS* synthetic lethality, and spatial-transcriptomic dissection of lactate metabolism in the TME. We additionally dedicate a section to artificial intelligence (AI)-driven and multi-omics approaches in PDAC metabolic research. Additionally, we connect metabolic biology to perioperative and surgical physiology, which have received limited attention in existing literature.

2. Metabolic reprogramming in pancreatic ductal adenocarcinoma tumor cells

2.1. The Warburg effect and oxidative phosphorylation

The Warburg effect was discovered in 1920s.¹⁸ In PDAC, oncogenic *KRAS* is the primary driver of enhanced glycolytic flux, transcriptionally upregulating glucose transporters (GLUT1, GLUT3) and key glycolytic enzymes.¹⁹ Beyond ATP generation, glycolytic intermediates feed the pentose phosphate pathway (PPP) and the hexosamine biosynthesis pathway.²⁰ Lactate exported via monocarboxylate transporter (MCT) acidifies the TME, suppressing anti-tumor immune responses and promoting invasion.²¹ Hypoxia is ubiquitous in PDAC. It amplifies glycolytic dependence through hypoxia-inducible factor-1 α -driven transcriptional programs.²² Despite the prominence of aerobic glycolysis, mitochondrial oxidative phosphorylation (OXPHOS) remains a critical

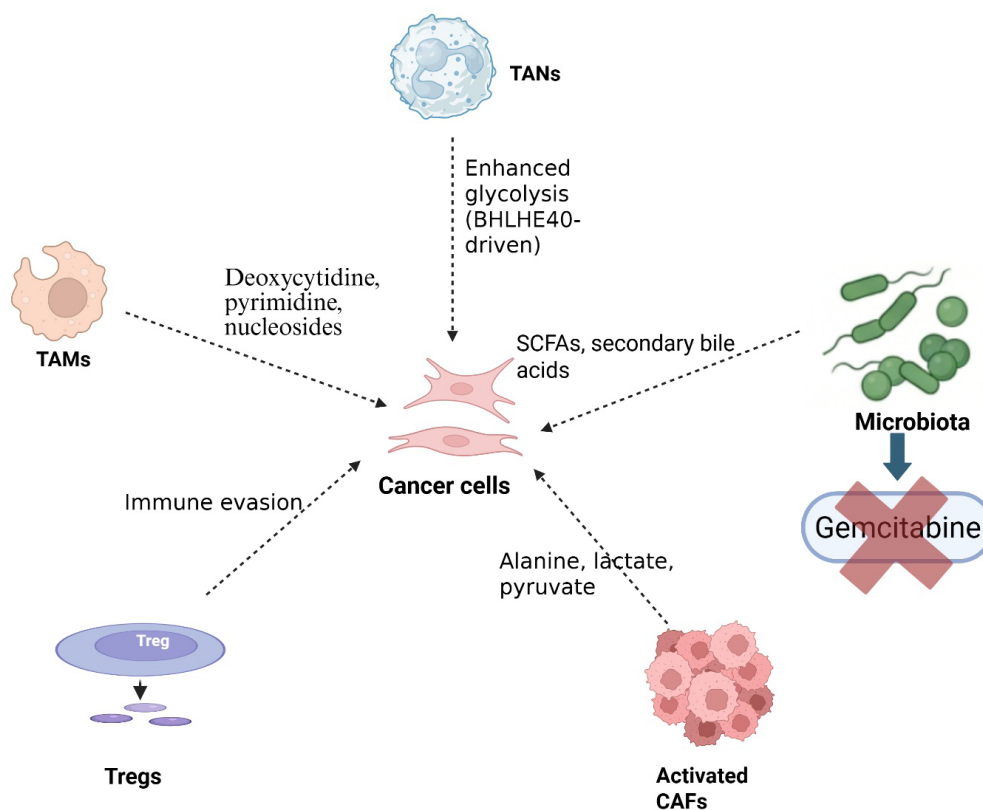


Figure 1. Metabolic crosstalk in the pancreatic ductal adenocarcinoma tumor microenvironment. In addition to tumor cells, the TME includes cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), tumor-associated neutrophils (TANs), regulatory T cells (Tregs), and the microbiota. These compartments interact through metabolic reprogramming and metabolite exchange to drive malignant behaviors and drug resistance. Schematic created with BioRender. Sun, S. (2026). <https://BioRender.com/o8y1ryd>

energy source in PDAC, particularly in glucose-limiting conditions.²³ PDAC cells display metabolic plasticity, dynamically shifting in response to nutrient availability and oncogenic context.²⁴ Recent evidence demonstrates that inhibition of Src-homology 2 domain-containing phosphatase 2/mitogen-activated protein kinase targeting the RAS pathway drives major mitochondrial alterations in PDAC, including elevated reactive oxygen species (ROS) that can be exploited therapeutically.²⁵ The reproducibility of this across different PDAC genetic backgrounds and its translatability to the human tumor remain to be confirmed. Moreover, upon *KRAS* inhibitor treatment, PDAC cells rapidly shift toward an OXPHOS-dependent drug-resistant state. However, depletion of the transcription factor ZBTB11 using molecular glue degraders can reprogram this metabolic resistance and resensitize cells to *KRAS* inhibition.²⁶ This finding, studied primarily in cell line and xenograft models, awaits validation in patient-derived organoids and patient cohort

before clinical translation can be considered.

2.2. Non-canonical glutamine metabolism

Glutamine is the most abundant free amino acid and is a critical nitrogen and carbon source for cancers.²⁷ Rather than converting glutamate to α -ketoglutarate, glutamine-derived aspartate is converted to oxaloacetate by glutamic-oxaloacetic transaminase 1 in PDAC cells. Then, it is converted to malate and pyruvate by malate dehydrogenase 1, generating nicotinamide adenine dinucleotide phosphate (NADPH) to sustain redox homeostasis.²⁸ This pathway is directly driven by *KRAS* through modulation of glutamic-oxaloacetic transaminase 1 and glutamate dehydrogenase 1. Inhibition of this cascade markedly suppresses PDAC growth. Pharmacological glutamine antagonism, exemplified by the DON prodrug derivative, potently suppresses PDAC in preclinical models.²⁹ Clinical evaluation of the glutaminase inhibitor telaglenastat has been pursued in solid tumors. The randomized phase II

CANTATA trial in metastatic renal cell carcinoma did not demonstrate improved progression-free survival with telaglenastat plus cabozantinib, underscoring the challenge of translating preclinical glutamine-targeting efficacy into clinical benefit.³⁰ PDAC-specific trials are warranted to determine whether glutamine-addicted PDAC subsets derive meaningful benefit from such strategies.

2.3. Lipid metabolism

Enhanced *de novo* lipogenesis, driven by upregulated fatty acid synthase (FASN) and sterol regulatory element-binding protein transcription factors, provides membrane lipids and signaling molecules for rapidly proliferating PDAC cells.³¹ In addition, elevated plasma cholesterol has been associated with increased PDAC risk, and high-cholesterol diets promote PDAC in animal models.³² Fatty acid oxidation serves as an alternative energy source under nutrient-deprived conditions, and lipid droplet accumulation provides both an energy reserve and signaling platform.³³ PIKfyve, a lipid kinase integral to lysosomal function, has recently been identified as a synthetic lethal vulnerability when combined with KRAS-mitogen-activated protein kinase inhibition, revealing novel lipid metabolic dependencies.³⁴ This synthetic lethal interaction was established in preclinical mouse and xenograft models. Clinical validation in PDAC patients and assessment of the therapeutic window are needed prior to clinical adoption. Targeting lipid metabolic enzymes, including FASN, ATP-citrate lyase (ACLY), acetyl-CoA carboxylase, and PIKfyve, represents an emerging therapeutic strategy in PDAC.³⁵

2.4. Macropinocytosis and nutrient scavenging

A distinguishing metabolic adaptation of KRAS-mutant PDAC cells is their capacity for macropinocytosis, bulk endocytic uptake of extracellular fluid and macromolecules via Rac1-dependent membrane ruffling.³⁶ Metabolomic analyses of human PDAC tumors confirmed that the TME is severely nutrient-poor, depleted of glucose, glutamine, and serine. PDAC cells actively scavenge extracellular protein, including albumin, to meet metabolic demands.³⁷ Macropinocytosed extracellular proteins are delivered to lysosomes and catabolized, yielding amino acids that fuel central carbon metabolism.³⁶

Pharmacological inhibition of macropinocytosis with the 5-(N-ethyl-N-isopropyl)amiloride (EIPA) suppresses KRAS-mutant tumor growth in preclinical models, identifying nutrient scavenging as a cancer-selective metabolic dependency.³⁸ The translational relevance of inhibiting macropinocytosis, however, remains to be fully explored. EIPA acts non-selectively across Na⁺/H⁺ exchangers that govern systemic pH and volume homeostasis, exerts effects beyond those attributable

to macropinocytosis blockade, and cannot achieve macropinocytosis-inhibitory concentrations in humans without toxicity.³⁹ No clinically applicable macropinocytosis inhibitor currently exists, and efforts to develop selective agents remain at an early preclinical stage.⁴⁰ Beyond tumor cells, CAFs also engage macropinocytosis in a calcium/calmodulin-dependent protein kinase kinase 2/Rho/Rac guanine nucleotide exchange factor 2-dependent manner to support their own metabolic fitness and to secrete amino acids that fuel tumor cells.⁴¹

3. Metabolic reprogramming in cancer-associated fibroblasts

Cancer-associated fibroblasts are the most abundant stromal cells in PDAC, orchestrating the dense desmoplastic stroma and creating physical barriers to drug delivery and immune cell infiltration.^{42,43} Paradoxically, studies depleting CAFs or stroma have not consistently improved survival, suggesting context-dependent and heterogeneous roles.⁴⁴ CAFs undergo profound metabolic reprogramming driven by signals from PDAC cells. A landmark study demonstrated that pancreatic stellate cells, the principal CAF subtype, secrete alanine via an autophagy-dependent mechanism actively stimulated by PDAC-derived cues. Pancreatic stellate cell-derived alanine outcompetes glucose and glutamine as a tricarboxylic acid (TCA) cycle carbon source in the nutrient-poor tumor core, fueling lipid and amino acid biosynthesis in PDAC cells.⁴⁵ This reverse Warburg-type metabolic symbiosis, in which CAFs engage aerobic glycolysis and catabolism to nourish tumor cells, creates a mutually sustaining ecosystem.⁴⁶ CAF-derived lactate, pyruvate, and other metabolic intermediates also support tumor cell OXPHOS.

Single-cell transcriptomic analyses have identified distinct CAF subtypes with unique metabolic phenotypes. Myofibroblastic CAFs exhibit enhanced glycolysis and extracellular matrix production, while inflammatory CAFs display distinct lipid and inflammatory metabolic signatures.⁴⁷ Leucine-rich repeat containing 15-positive CAFs define an additional immunosuppressive subset associated with poor immunotherapy response.⁴⁸ Targeting CAF metabolism by disrupting lactate transport, autophagic alanine secretion, or lipid metabolic programs offers dual benefits of impairing tumor metabolic supply lines and disrupting immunosuppressive architecture.

4. Metabolic reprogramming in tumor-associated neutrophils

Tumor-associated neutrophils are significant contributors to PDAC pathobiology. High TAN abundance is associated with poor prognosis, and TANs exert predominantly

pro-tumorigenic roles through immune suppression, promotion of angiogenesis, and facilitation of metastasis.⁴⁹ However, the prognostic value of TAN quantity varies across studies. Cohort size, scoring methodology, and the lack of standardized markers to distinguish pro-tumor from anti-tumor subsets continue to limit the clinical interpretability of TAN. The functional landscape of TANs in PDAC is highly heterogeneous, reflecting neutrophil plasticity under different TME conditions.⁵⁰

Single-cell RNA sequencing has begun to dissect TAN heterogeneity at unprecedented resolution. Zeng *et al.*⁵¹ identified seven distinct TAN subpopulations in the PDAC TME, each with characteristic transcriptional and metabolic signatures. A subpopulation marked by macrophage migration inhibitory factor expression was identified as a novel prognostic TAN marker.⁵¹ Metabolically, pro-tumorigenic TANs exhibit enhanced glycolytic activity driven by BHLHE40 transcription factor upregulation, supporting their survival and immunosuppressive functions within the glucose-depleted TME.⁵⁰ Targeting TAN-specific metabolic programs may offer strategies to reprogram TANs toward anti-tumor phenotypes. These TAN metabolic subsets have so far been characterized in only a limited number of cohorts. Independent multi-center validation, together with the development of clinically deployable markers, will be required before such subsets can guide patient stratification for therapy.

5. Metabolic reprogramming in tumor-associated macrophages

Tumor-associated macrophages constitute a major immune cell component of the PDAC TME and exert predominantly immunosuppressive, pro-tumorigenic effects.⁵² TAM depletion inhibits tumor progression in preclinical PDAC models.⁵³ M1-polarized macrophages rely on enhanced glycolysis and nitric oxide production for pro-inflammatory functions. On the other hand, M2-polarized TAMs, which predominate in the PDAC TME, preferentially utilize OXPHOS and fatty acid oxidation to support anti-inflammatory and tissue-remodeling activities.⁵⁴ Oncometabolites and hypoxia within the PDAC TME actively skew macrophage polarization toward the M2 phenotype, creating a self-reinforcing immunosuppressive circuit.⁵⁵

A study by Halbrook *et al.*⁵⁶ revealed that M2-polarized TAMs release pyrimidine nucleosides, specifically deoxycytidine, into the TME. These nucleosides are taken up by PDAC cells and competitively inhibit gemcitabine phosphorylation, directly linking TAM metabolism to chemotherapy resistance.⁵⁶ Additional TAM metabolic

adaptations include arginase-1-mediated arginine depletion that impairs T cell activation, upregulated prostaglandin E2 synthesis that suppresses immunity, and altered iron metabolism that supports tumor growth.⁵⁷ Therapeutic approaches targeting TAM metabolism include colony-stimulating factor 1 receptor inhibitors, C-C chemokine receptor 2 antagonists, and reprogramming strategies using succinate or itaconate analogs.^{58,59}

6. Energy metabolism-associated post-translational modifications in pancreatic ductal adenocarcinoma tumor microenvironment

Metabolism does not act solely as an energy provider. Glycolytic and TCA cycle intermediates serve as direct substrates for post-translational modifications. Lactate is the substrate for lysine lactylation (Kla). Acetyl-CoA fuels lysine acetylation. These post-translational modifications link the nutrient state of a cell to its transcriptional signaling and act as a key interface between metabolic reprogramming and immune evasion in tumors. Lactate is recognized as a substrate for Kla on both histone and non-histone proteins. In the lactate-rich PDAC TME, Kla is markedly elevated and tracks with an immunosuppressive phenotype. Yang *et al.*⁶⁰ recently described a histone lactylation-driven feedback loop in PDAC. Tumor-derived cholesterol is delivered to TAMs via small extracellular vesicles, thereby reinforcing M2 polarization and immunosuppression.⁶⁰ Sun *et al.*⁶¹ also showed that lactate induces K63-linked lactylation of endosulfine α in PDAC cells, thereby activating signal transducer and activator of transcription 3/C-C motif chemokine ligand 2 signaling. The resulting secretion of C-C motif chemokine ligand 2 recruits TAMs to the tumor, and lactate reprograms them to an immunosuppressive phenotype. Glycolytic inhibition or mutant-*KRAS* targeting can suppress lactate production in preclinical PDAC models. This may lower global lactylation and restore sensitivity to immune checkpoint blockade in PDAC.^{61,62} Acetyl-CoA generated from glycolysis, fatty acid oxidation, and glutaminolysis fuels histone and non-histone acetylation through p300/CREB-binding protein. Sirtuins can deacetylate these proteins in an NAD⁺-dependent manner. In PDAC, oncogenic *KRAS* elevates the cellular acetyl-CoA pool via protein kinase B-*ACLY* signaling.⁶³ These metabolic shifts remodel the acetylome of tumor and stromal cells, modulating metabolic enzyme activity and chromatin accessibility.⁶⁴ Collectively, these post-translational modifications can be targeted by interfering with the enzymes and metabolite pools that sustain them. Possible strategies include blocking lactate export, inhibiting writers such as p300, or

interfering with site-specific lactylation events.

7. Metabolic reprogramming of T cells in the tumor microenvironment

T cells, particularly CD8⁺ T cells, are the main mediators of anti-tumor adaptive immunity. Their high infiltration predicts significantly better prognosis in PDAC.⁶⁵ However, the PDAC TME presents formidable physical and metabolic barriers to T cells.⁶⁶ Within the TME, competition for glucose between tumor cells and T cells leads to T-cell metabolic deprivation. Simultaneously, the accumulation of lactate, kynurenine, and adenosine directly impairs T cell function and drives exhaustion.^{67,68} The indoleamine 2,3-dioxygenase 1 (IDO1)–kynurenine–aryl hydrocarbon receptor axis is a critical immunometabolic checkpoint in PDAC. IDO1 upregulation by tumor cells and stromal cells converts tryptophan to kynurenine, which activates the aryl hydrocarbon receptor, promotes Treg differentiation, and inhibits cytotoxic T cell proliferation.⁶⁹ Similarly, the CD39–CD73 adenosine pathway generates immunosuppressive extracellular adenosine that suppresses T cell and natural killer cell activity via A2A receptor signaling.⁷⁰ CD73-dependent adenosine signaling has been shown to drive immunosuppression in a molecular subtype of PDAC, and CD73 inhibition combined with programmed cell death protein 1 (PD-1) blockade restores anti-tumor immunity.⁷¹

Regulatory T cells are enriched in PDAC and suppress cytotoxic T cells through interleukin-10 and transforming growth factor beta secretion, direct cytotoxicity, and inhibitory crosstalk with tumor-associated dendritic cells.⁷² Unlike effector T cells, Tregs are better adapted to glucose-poor, lactate-rich TME, conferring a metabolic survival advantage.⁷³ Therapeutic strategies to rescue T cell metabolism include IDO1 inhibitors, CD39–CD73 inhibitors, Treg depletion, and mechanistic target of rapamycin pathway modulators that enhance effector T cell metabolic fitness.

8. Metabolic reprogramming of the intratumoral microbiota

The intratumoral microbiota of PDAC, derived from oral and intestinal sources, constitutes a biologically significant component of the TME. Distinct microbial compositional signatures have been associated with differences in PDAC patient survival, suggesting the microbiota may influence tumor biology and treatment response.⁷⁴ The intestinal microbiota has been implicated in modulating immunotherapy responses. Fecal microbiota transplant from responder donors decreases resistance to anti-PD-1 therapy.⁷⁵ Analogous mechanisms may operate in PDAC, where bacteria can metabolize gemcitabine and alter its

anti-tumor efficacy.⁷⁶

Intratumoral bacteria engage in metabolic activities that shape the local TME, generating short-chain fatty acids and other metabolites that modulate immune cell function and tumor cell behavior.⁷⁷ One study demonstrated that the intratumoral microbiome composition predicts long-term survival in PDAC patients, and that tumor microbiome-derived metabolites influence immune cell infiltration patterns.⁷⁸ The microbiome may be modulated therapeutically through dietary interventions, antibiotics, prebiotics, and fecal microbiota transplant, offering potentially accessible avenues to reshape the PDAC TME.⁷⁹ However, this pathway has been demonstrated primarily in preclinical models to date. Its clinical relevance and the contribution of specific bacterial taxa remain to be defined. Whether antibiotic intervention can durably restore gemcitabine sensitivity in patients also needs to be established in clinical trials.

9. Metabolic reprogramming and early oncogenic events in pancreatic ductal adenocarcinoma

Metabolic reprogramming is not merely a feature of established PDAC but an active driver of early oncogenic events. Metastatic dissemination can occur at surprisingly early stages of disease, even before invasive cancer is detectable.⁸⁰ The acinar-to-ductal metaplasia (ADM) program, widely considered to represent the cellular origin of PDAC, is intimately linked to metabolic reprogramming. Oncogenic *KRAS* expression is enough to drive ADM and subsequent PanIN formation.⁸¹ During ADM, oncogenic *KRAS* alters mitochondrial metabolism in acinar cells, increasing mitochondrial ROS that drives their dedifferentiation toward a duct-like progenitor phenotype.⁸²

The relationship between chronic pancreatitis and PDAC is bidirectional. Chronic pancreatitis predisposes to PDAC, while PDAC can itself present with pancreatitis as an early manifestation.⁸³ Inflammation-driven pancreatitis establishes a metabolically activated stromal environment permissive for malignant transformation.⁸⁴ Targeting early metabolic vulnerabilities in PanIN lesions, potentially coupled with liquid biopsy-based early detection strategies, may enable chemoprevention of PDAC.^{85,86} These early metabolic shifts are not only mechanistic drivers but also potential windows for detection. Glycolytic activation in PanIN and early PDAC lesions underlies the value of ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography imaging in early detection of PDAC.⁸⁷ Similarly, more advanced metabolic imaging modalities, such as hyperpolarized ¹³C-pyruvate magnetic

resonance imaging, can provide higher-resolution, real-time readouts of tumor glycolytic activity.⁸⁸

Circulating metabolic biomarkers offer another direction. In a prospective study, plasma branched-chain amino acids were elevated before PDAC diagnosis, reflecting systemic protein catabolism driven by occult disease.⁸⁹ Metabolomic analysis of pancreatic cyst fluid can also help to stratify malignant potential in intraductal papillary mucinous neoplasms.⁹⁰ Integrating these metabolism-derived signals with *KRAS*-mutant circulating tumor DNA, cancer antigen 19-9, and AI-driven multi-omic models may enable better screening and early diagnosis. Aside from metabolic imaging, advances in molecular imaging now allow visualization of immune checkpoint molecules within the TME. For example, near-infrared fluorescence and Cerenkov luminescence dual-modality imaging has been used to compare programmed death-ligand 1-specific and non-specific antibody tracer uptake in preclinical tumor models.⁹¹ This could inform the design of antibody-based imaging probes for the microenvironment. Translating such approaches to PDAC could further refine *in situ* assessment of immunometabolic heterogeneity.

10. Metabolic reprogramming network and autophagy

Autophagy, lysosomal recycling of intracellular components, suppresses tumorigenesis in non-transformed cells by eliminating dysfunctional organelles and misfolded proteins. However, in established tumors, autophagy is co-opted as a pro-survival strategy.⁹² PDAC cells exhibit high levels of basal autophagy driven by oncogenic *KRAS* and the nutrient-poor TME. Autophagic recycling provides amino acids, fatty acids, and nucleotides redirected into central metabolic pathways.⁹³ Autophagy is important during nutrient starvation.⁹⁴ Autophagy inhibition with hydroxychloroquine in combination with chemotherapy has been evaluated in a randomized clinical trial, though results demonstrated no significant improvement in advanced PDAC.⁹⁵ As noted, CAFs engage autophagy to secrete alanine fueling PDAC metabolism.⁴⁵ TAMs also rely on autophagic pathways for polarization-state transitions.⁹⁶ Recent advances in selective autophagy pathways, mitophagy, lipophagy, and ferritinophagy, also reveal additional metabolic regulation.⁹⁷ Extracellular signal-regulated kinase inhibition has been shown to enhance hydroxychloroquine-mediated autophagy inhibition, identifying a rational combination strategy.⁹⁸

Although the preceding sections describe glycolysis, glutamine metabolism, lipid metabolism, macropinocytosis, and autophagy individually, these

pathways do not operate in isolation but are integrated into a metabolic network to some degree.⁹⁹ First, oncogenic *KRAS* serves as the common upstream driver, simultaneously upregulating glycolytic flux, the glutamine pathway, *de novo* lipogenesis, macropinocytic scavenging, and basal autophagy.¹⁰⁰ These pathways also feed a shared pool of central carbon intermediates. Glycolysis, glutaminolysis, macropinocytic protein catabolism, and autophagic recycling all supply acetyl-CoA and TCA cycle carbon, which is in turn fed into lipid biosynthesis. This links separate pathways through a common metabolite currency. Additionally, several of these routes are unified by their role in maintaining redox balance, as the pentose phosphate pathway and serine metabolism all converge on NADPH production to reduce oxidative stress.⁹⁹ Viewing PDAC metabolism as an integrated, largely *KRAS*-driven network therefore may provide a unifying framework that connects the individual adaptations.

11. Therapeutic strategies targeting metabolic vulnerabilities

Only about 20% of PDAC patients are eligible for surgical resection at diagnosis⁶ (Figure 2). Gemcitabine, a drug that incorporates into nascent strands and depletes deoxyribonucleotide pools via ribonucleotide reductase inhibition, remains a chemotherapy pillar.¹⁰¹ FOLFIRINOX demonstrates superior efficacy over gemcitabine in some patients but is associated with substantial toxicity.⁵ For the subset of patients eligible for surgical resection, the procedure itself imposes significant metabolic consequences that shape subsequent treatment considerations. Pancreaticoduodenectomy fundamentally alters systemic metabolic physiology. Postoperative complications, including pancreatic fistula, further complicate recovery.¹⁰² Inhibiting upregulated glycolysis represents an attractive strategy. GLUT1/3 transport inhibitors, hexokinase inhibitors (including 2-deoxy-D-glucose), pyruvate kinase M2 modulators, and lactate dehydrogenase A inhibitors are under investigation.¹⁰³ Lactate transport inhibition disrupting MCT1/4 impairs both tumor lactate export and the metabolic symbiosis with CAFs.¹⁰⁴ Blocking hypoxia-inducible factor α -driven glycolytic upregulation in hypoxic PDAC cells may provide another avenue.²² Pharmacological glutamine antagonism with DON prodrug derivatives has demonstrated potent anti-tumor activity in PDAC, including significant tumor growth decrease in mouse models.²⁹ Combining glutamine antagonism with immune checkpoint inhibitors simultaneously may starve tumor cells and enhance immune cell function. Glutaminase inhibitors such as telaglenastat have been evaluated clinically in advanced solid tumors, though single-agent activity has been

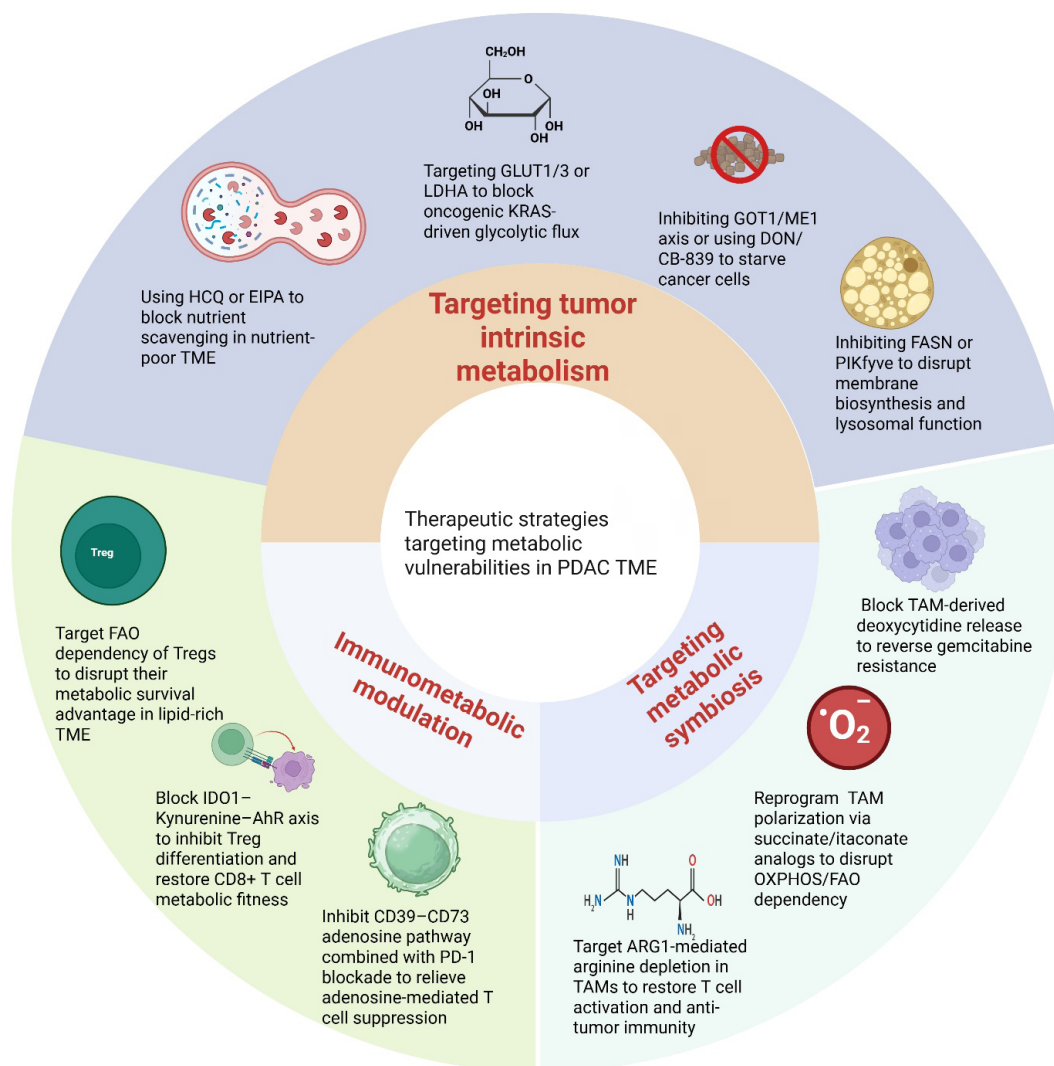


Figure 2. Targeting metabolic vulnerabilities in the pancreatic ductal adenocarcinoma tumor microenvironment. Key therapeutic interventions include inhibiting tumor-intrinsic metabolism, disrupting metabolic symbiosis, and immunometabolic modulation to reverse the immunosuppressive microenvironment. Schematic created with BioRender. Sun, S. (2026). <https://BioRender.com/7otuezq>.

Abbreviations: AhR: Aryl hydrocarbon receptor; ARG1: Arginase 1; CD39: Cluster of differentiation 39; CD73: Cluster of differentiation 73; DON: 6-Diazo-5-oxo-L-norleucine; EIPA: Ethylisopropylamiloride; FAO: Fatty acid oxidation; FASN: Fatty acid synthase; GLUT1/3: Glucose transporter 1/3; GOT1: Glutamic-oxaloacetic transaminase 1; HCQ: Hydroxychloroquine; IDO1: Indoleamine 2,3-dioxygenase 1; KRAS: Kirsten rat sarcoma viral oncogene homolog; LDHA: Lactate dehydrogenase A; ME1: Malic enzyme 1; OXPHOS: Oxidative phosphorylation; PD-1: Programmed cell death protein 1; PDAC: Pancreatic ductal adenocarcinoma; PIKfyve: Phosphoinositide kinase, FYVE-type zinc finger containing; TAM: Tumor-associated macrophage; TME: Tumor microenvironment; Treg: Regulatory T cell.

modest.¹⁰⁵

Fatty acid synthase, ACLY, and ACC inhibitors impair membrane biosynthesis and signaling in PDAC cells.³⁵ Statins, which inhibit the mevalonate pathway, have been associated with improvements in PDAC outcomes in epidemiological data.¹⁰⁶ PIKfyve inhibition in combination with KRAS–mitogen-activated protein kinase inhibition

induces synthetic lethality through metabolic crisis.³⁴ KRAS G12D and G12V inhibitors, which predominate in PDAC, are in clinical development following the success of G12C inhibitors in lung cancer.¹⁰⁷ RAS pathway inhibition induces mitochondrial alterations. Combined KRAS and ferroptosis induction shows preclinical synergy.²⁵ Upon KRAS inhibitor treatment, PDAC cells shift toward

OXPHOS-dependent resistance, driven by ZBTB11 upregulation. ZBTB11 degradation with a molecular glue resensitizes cells.²⁶ Combining KRAS inhibitors with autophagy inhibitors, antioxidants, or glutamine pathway blockers represents a rational strategy.

Because the same metabolic activity that fuels PDAC cells also enforces local immunosuppression, metabolic targeting and immune checkpoint blockade are mechanistically complementary. Depleting an immunosuppressive metabolite can convert a checkpoint-refractory cold tumor into one in which PD-1/programmed death-ligand 1 blockade becomes effective.¹⁰⁸ Three metabolic axes illustrate both the promise of this logic and the gap between preclinical theory and clinical efficacy. Their complement explains why most metabolism-immunotherapy combinations have so far failed to translate into clinical benefit. The tryptophan-kynurenine pathway is the first axis. IDO1 degrades tryptophan to immunosuppressive kynurenine.⁶⁹ The selective IDO1 inhibitor epacadostat restored anti-tumor T cell immunity and synergized with PD-1 blockade in the early-phase ECHO-202 study. The randomized phase III ECHO-301 trial, however, failed.¹⁰⁹ The adenosine pathway axis has generated encouraging PDAC-specific evidence to date. CD73 catalyzes the terminal step of extracellular adenosine production and is overexpressed in roughly 40–60% of PDAC, where it suppresses CD8⁺ T and natural killer cell activity through A2A receptor signaling.⁷¹ In the randomized phase Ib ARC-8 trial, the CD73 inhibitor quemliclustat, added to gemcitabine and nab-paclitaxel, produced an objective response rate of approximately 41% and a median overall survival of approximately 21 months in treatment-naïve metastatic PDAC. But adding the anti-PD-1 antibody zimberelimab did not clearly augment benefit, and the mechanisms remained to be explored.¹¹⁰

These data support the ongoing placebo-controlled phase III PRISM-1 trial of quemliclustat with chemotherapy, which represents one of the major metabolic-immunomodulatory agents reaching phase III in PDAC. Complementary adenosine pathway agents, including the anti-CD39 antibody TTX-030, are likewise being advanced, reinforcing this axis as a promising immunometabolic target in PDAC.¹¹¹ Glutamine antagonism is another example of this dual rationale, since blocking glutamine starves the tumor while boosting the metabolic fitness of effector T cells. The first-generation antagonist DON sensitized PDAC models to anti-PD-1 therapy but failed clinically owing to gastrointestinal toxicity. Its prodrug, sirpiglenastat (DRP-104), was engineered to deliver the active drug within the tumor. It enhanced checkpoint blockade in preclinical PDAC and has been evaluated in

early-phase trials.¹¹² Viewed together, these trials reveal a consistent pattern. Combinations of metabolism-targeting and immunotherapy have most often failed not because the metabolic target was wrong, but for other reasons. Metabolic pathways have many complementary, redundant routes, and it is difficult to confirm whether an inhibitor truly suppresses its target and how effectively it does so.

The clinical track of metabolic targeting in PDAC can be grouped into three categories. The first category comprises clear failures. The glutaminase inhibitor telaglenastat did not improve progression-free survival in the randomized CANTATA trial.³⁰ Autophagy inhibition with hydroxychloroquine plus chemotherapy showed no significant benefit in the randomized study.⁹⁵ The IDO1 inhibitor epacadostat failed in the phase III ECHO-301 trial. The first-generation glutamine antagonist DON was abandoned because of dose-limiting gastrointestinal toxicity. The second comprises ongoing programs. The CD73 inhibitor quemliclustat produced an encouraging response rate and overall survival in the phase Ib ARC-8 trial, and is now being tested in the phase III PRISM-1 trial.¹¹⁰ Other adenosine-pathway agents, such as the anti-CD39 antibody TTX-030, and the tumor-targeted DON prodrug sirpiglenastat (DRP-104) remain in early-phase evaluation. Unequivocally successful metabolism-directed agents remain essentially empty in PDAC, though. Closest examples are the antimetabolite backbones gemcitabine and FOLFIRINOX, which target nucleotide and DNA metabolism but were developed empirically rather than from rational metabolic-pathway design.¹⁰¹ Several reasons explain why so few promising metabolic targets have translated into clinical benefit. Metabolic pathways are highly redundant, so inhibiting one node is compensated for by compensatory flux rerouting. Moreover, many inhibitors lack pharmacodynamic biomarkers, making it difficult to confirm whether the intended target is actually suppressed in patients.

The obstacle to clinical translation of metabolism-targeted therapy is the overlap between the metabolic programs of tumor cells and those of proliferating or metabolically active normal tissues. This narrows the therapeutic window and raises the risk of on-target, off-tumor toxicity.¹¹³ Pathways exploited by PDAC cells, including glycolysis, glutamine catabolism, nucleotide synthesis, and autophagy, are also indispensable for hematopoietic, gastrointestinal, hepatic, and immune cells. Consequently, systemic inhibition frequently produces dose-limiting toxicities.¹¹⁴ This pattern is already evident among agents discussed above. The first-generation glutamine antagonist DON, despite robust preclinical efficacy, was limited clinically because of gastrointestinal

toxicity. Consequently, the development of tumor-targeted prodrugs such as sirpigenastat (DRP-104) was designed to widen the therapeutic margin.¹¹⁵ Similarly, the macropinocytosis inhibitor EIPA cannot reach macropinocytosis-inhibitory concentrations in humans without unacceptable toxicity. Autophagy inhibition with hydroxychloroquine is also constrained by the essential role of basal autophagy in normal tissues.¹¹⁶

12. Metabolic heterogeneity and therapeutic resistance

Metabolic phenotypes differ markedly between patients. This inter-patient heterogeneity is connected with established transcriptomic subtypes of PDAC. Broad metabolite profiling has resolved PDAC into distinct metabolic subtypes, including glycolytic, lipogenic, and slow-proliferating classes that display differential sensitivity to inhibitors of glycolysis, lipogenesis and redox pathways.¹¹⁷ These metabolic classes are not independent of molecular subgroups. The lipogenic subtype aligns with the classical transcriptomic signature, whereas the glycolytic subtype corresponds to the more aggressive quasi-mesenchymal subtype. Karasinska *et al.*¹¹⁸ confirmed this in a large multi-cohort series.¹¹⁸ They stratified tumors along the glycolysis–cholesterol synthesis axis. Glycolytic tumors carried the shortest survival. Cholesterogenic tumors carried the best. Glycolytic gene expression was enriched in *KRAS*- and *MYC*-amplified tumors. The practical implication is that metabolic targeting is unlikely to succeed as a one-size-fits-all approach. Instead, biomarker-driven selection that matches a given metabolic inhibitor to the dominant metabolic subtype of an individual tumor will be required.

A central reason for the resistance of both targeted and cytotoxic therapy in PDAC is metabolic plasticity. When one metabolic or oncogenic pathway is pharmacologically blocked, PDAC cells reroute metabolic flux toward compensatory pathways that restore biosynthetic capacity and energy supply, thereby escaping treatment. This adaptive rewiring is an active resistance mechanism. Dissecting how it operates is essential for designing durable combinations. For example, serine metabolism serves as an adaptive node sustaining redox homeostasis under therapeutic stress. PDAC cells exposed to redox-disrupting agents survive by upregulating *de novo* serine biosynthesis and uptake, which supports NADPH-dependent antioxidant defense, nucleotide synthesis, and epigenetic regulation. This resilience blunts the efficacy of single agents and is useful only when serine adaptation is co-targeted.¹¹⁹

In addition, flux can be redirected into the PPP, conferring resistance to targeted therapy. Erlotinib-resistant PDAC cells downregulate glycolysis and upregulate the PPP enzyme glucose-6-phosphate dehydrogenase, elevating the NADPH/NADP⁺ ratio to neutralize ROS. PPP inhibition raises ROS, induces cell cycle arrest, and resensitizes resistant cells, demonstrating that the resistance-conferring metabolic state is itself a targetable vulnerability.¹²⁰ Mitochondrial plasticity provides a further escape route, as dysregulated mitochondrial dynamics and mitophagy allow PDAC cells to preserve OXPHOS and redox capacity under therapeutic pressure, contributing to treatment resistance.¹²¹

13. Artificial intelligence in pancreatic ductal adenocarcinoma metabolic research

Artificial intelligence has transformed PDAC research across multiple domains. AI-driven drug discovery platforms have identified synergistic drug combinations targeting metabolic vulnerabilities, substantially accelerating discovery compared to traditional high-throughput screening.¹²² The Molecular Twin platform uses AI to predict prognosis and therapeutic response for individual PDAC patients.¹²³ Combining computed tomography and magnetic resonance imaging data, multimodal machine learning algorithms have been developed to evaluate the risk of malignant transformation in pancreatic cystic neoplasms with high accuracy, providing a non-invasive screening pathway.¹²⁴ Single-cell and spatial multi-omics technologies enable unprecedented resolution of metabolic heterogeneity within the PDAC TME, revealing cell-type-specific metabolic signatures and novel crosstalk axes. For example, integrated single-cell and spatial transcriptomic analysis has resolved lactate metabolism-associated cell subtypes and their interactions.¹²⁵ AI-driven biomarker discovery beyond cancer antigen 19-9, including metabolomic signatures, may enable earlier PDAC detection and patient stratification.¹²⁶

Artificial intelligence and multi-omics integration have emerged as promising approaches for dissecting the metabolic complexity of the PDAC TME. AI-driven pipelines can be applied to metabolic questions. These include resolving cell-type-specific metabolic signatures, mapping metabolic crosstalk between compartments, and identifying candidate metabolic vulnerabilities. Single-cell and spatial multi-omics datasets, which are difficult to analyze with conventional methods, can now be analyzed using such computational frameworks to reveal metabolic heterogeneity with high resolution. Several AI-derived metabolic predictions in PDAC have advanced beyond

in silico to biological and clinical validation. A complete example is the graph deep learning model DeepMeta, which predicts sample-specific metabolic dependencies from transcriptomic and metabolic network information. DeepMeta predicted that PDAC-relevant *CTNNB1*-activating mutations confer dependency on nucleotide metabolism. This prediction was then experimentally confirmed, as pharmacological inhibition and short hairpin RNA knockdown of these enzymes selectively suppressed *CTNNB1*-mutant cells, with ¹³C-glucose tracing demonstrating increased nucleotide-pathway flux.¹²⁷ A machine learning-derived metabolism-related signature, built by integrating 112 metabolic pathways across more than 1,000 PDAC patients, predicted immunotherapy response and prognosis and was validated in an in-house cohort using immunohistochemistry and functional assays.¹²⁸ The Molecular Twin platform similarly integrates multi-omic data to predict outcomes for individual PDAC patients. In addition, a framework of machine learning, using generative adversarial networks, distinguished malignant from normal metabolic states with high accuracy and pointed dysregulated heparan sulfate degradation, O-glycan metabolism, and coordinated fatty acid transport as PDAC metabolic features.¹²⁶ AI-enabled integration of multi-omics, imaging, and spatial data is likewise being explored to define immunometabolic PDAC subtypes relevant to therapy selection. Nonetheless, the translational potential of these approaches remains uneven. Many AI-derived metabolic signatures have been characterized in single cohorts or rest on computational prediction alone, and the underlying biological mechanisms are often only partially validated.

14. Current status and future perspectives

Not all metabolic alterations described above carry equal clinical actionability. An explicit prioritization helps translate this complexity into a practical roadmap. Three groups can be proposed based on the maturity of clinical evidence and druggability. The first group comprises the most actionable targets in PDAC. The adenosine axis is the leading example. The CD73 inhibitor, queclinstat, has advanced to the phase III PRISM-1 trial because of encouraging phase Ib survival data.¹¹⁰ Mutant *KRAS* itself, now druggable with G12D and G12V inhibitors, also belongs in this group, together with the antimetabolite backbones gemcitabine and FOLFIRINOX, which remain the clinical standard.⁵ The second group comprises targets with strong mechanistic and preclinical rationale but only with early-phase clinical data. These include glutamine antagonism with tumor-targeted prodrugs such as sirpigenastat, lactate transport via MCT1/4, and lipogenic enzymes including FASN and ACLY. Their success will

depend on patient selection based on metabolic subtype rather than on unselected use. The third group comprises targets that are mechanistically compelling but currently lack a clinically viable agent. Macropinocytosis inhibition exemplifies this group. No selective, systemically tolerable inhibitor yet exists. *KRAS*-inhibitor resistance nodes such as ZBTB11 and PIKfyve/*KRAS* synthetic lethality are promising but rest on laboratory observations awaiting validation.

Pancreatic ductal adenocarcinoma is a profoundly heterogeneous disease at both inter-patient and intra-tumoral levels, with metabolic programs evolving dynamically through the disease trajectory. Metabolic plasticity, the capacity of PDAC cells to shift between metabolic states in response to therapy, poses a major challenge. Inhibiting one pathway frequently results in compensatory upregulation of alternatives.²⁴ Rational combination strategies that simultaneously block multiple metabolic routes, exploit oncogene-specific synthetic lethality, and employ biomarker-driven patient selection will be essential. Key future directions span several interconnected domains. Clinical translation of *KRAS* inhibitors combined with metabolic targeting agents remains a primary focus, alongside the development of validated metabolic biomarkers for patient stratification. Microbiome modulation to reshape the immunometabolic TME, AI-powered identification of synthetic lethal metabolic vulnerabilities, and the integration of metabolic reprogramming approaches with novel immunotherapy modalities including cancer vaccines also represent further promising avenues.¹²⁹ The convergence of mechanistic understanding, technological innovation, and clinical translation positions metabolic targeting as a central pillar of next-generation PDAC therapy. In addition, more evidence for recently reported metabolic vulnerabilities is warranted. Several findings highlighted in this review, including ZBTB11-mediated OXPHOS resistance to *KRAS* inhibitors²⁶, PIKfyve/*KRAS* synthetic lethality³⁴, BHLHE40-driven TAN glycolytic reprogramming⁵⁰, and the macrophage migration inhibitory factor-positive TAN prognostic subset⁵¹ have been reported within the past one to two years and rely predominantly on laboratory observations. While these results are mechanistically hopeful and have generated great interest, their reproducibility in independent patient cohorts has yet to be established. That said, this work provides new directions regarding targeting tumor metabolism in PDAC.

15. Conclusion

Pancreatic ductal adenocarcinoma remains a lethal human malignancy. By integrating recent advances across tumor cells, stromal and immune compartments,

the microbiome, and emerging AI-enabled analytical frameworks, the present review offers a cross-compartment perspective that complements existing compartment-specific or nutrient-focused syntheses. Taken together, the evidence synthesized here reveals that the unique metabolic landscape of PDAC, characterized by extensive reprogramming of glucose, glutamine, lipid, macropinocytic, and autophagic metabolism in tumor cells, and by complex metabolic crosstalk with CAFs⁴⁵, TAMs⁵⁸, TANS⁵⁰, T lymphocytes⁶⁷, and intratumoral microbiota⁷⁹, is a driver of progression. Each cellular compartment of the TME exhibits characteristic metabolic reprogramming that contributes to the immunosuppressive, desmoplastic, and chemoresistant phenotype of PDAC. Understanding and targeting these metabolic interactions, individually and in rational combination, represents a compelling and increasingly tractable therapeutic strategy. Emerging technologies, including single-cell transcriptomics, spatial metabolomics, and AI-driven analytics,¹²³ are accelerating discovery of novel metabolic vulnerabilities. Continued investment in basic research and translational studies will be essential to translate these advances into improvements in patient outcomes.

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Author contributions

Conceptualization: Pan Zhao, Yanzhen Xu, Zhibo Zuo
Visualization: Xiaoying Tao, Junjun Du, Xiangyun He
Writing—original draft: Silin Xiang, Shuai Sun
Writing—review & editing: Nan Li, Rongjing Zhou, Xu Mao

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