Trends in Molecular Medicine

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Review

Exploiting pancreatic cancer metabolism: challenges and opportunities

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Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive form of pancreatic cancer, known for its challenging diagnosis and limited treatment options. The focus on metabolic reprogramming as a key factor in tumor initiation, progression, and therapy resistance has gained prominence. In this review we focus on the impact of metabolic changes on the interplay among stromal, immune, and tumor cells, as glutamine and branched-chain amino acids (BCAAs) emerge as pivotal players in modulating immune cell functions and tumor growth. We also discuss ongoing clinical trials that explore metabolic modulation for PDAC, targeting mitochondrial metabolism, asparagine and glutamine addiction, and autophagy inhibition. Overcoming challenges in understanding nutrient effects on immune–stromal–tumor interactions holds promise for innovative therapeutic strategies.

Highlights

Tumor and its immune microenvironment metabolism emerge as critical hallmarks that should be considered in the design and application of novel therapeutic drugs in pancreatic cancer.

The heterogeneity of pancreatic cancer metabolism, and the different metabolic behavior between primary tumors and metastasis, pose a challenge to the effectiveness of existing treatments.

The synthesis of polyamines using glutamine as a main source is emerging as a key feature of pancreatic cancer.

The targeting of tumor metabolism may help in reprograming the tumor immune microenvironment (TIME) and promoting the response to immunotherapy.

Pancreatic cancer and its evolving metabolic landscape

PDAC is an aggressive malignancy ranking among the deadliest of all cancers, with a 5-year survival rate of merely 10%, emphasizing the critical need for a deeper understanding of its underlying biology [1,2]. In recent years there has been a surge of interest and research in the metabolic features of pancreatic cancer. This focus arises from compelling evidence suggesting that metabolic reprogramming plays a pivotal role in tumor initiation, progression, and therapy resistance [3].

As our understanding of the metabolic intricacies within pancreatic cancer continues to expand, this topic has gained unprecedented relevance, promising new avenues for early detection, therapeutic targeting, and personalized medicine in the fight against this dismal disease. In this review article we delve into the latest developments in the field, shedding light on the metabolic signatures and their potential implications for clinical practice and research endeavors. We explore herein PDAC tumor metabolism, emphasizing key alterations driving progression and therapy resistance and metabolic changes in the **tumor immune microenvironment (TIME)** (see Glossary) to boost antitumor immunity. Finally, ongoing clinical trials using antimetabolic drugs are examined, offering new avenues for PDAC care.

Metabolic reprogramming stands as a critical axis in the battle against PDAC, offering promising avenues for therapeutic intervention and improved patient outcomes.

Metabolic characteristics of PDAC tumors

Pancreatic cancer rewires its metabolism to meet energy demands, relying on glucose, glutamine metabolism, and scavenging pathways, mediated primarily by the **RAS** pathway [4] (Figure 1). KRAS mutations lead to persistent downstream signaling pathways, such as Raf/Mek/Erk, PI3K/Pdk1/Akt, and Ral, driving cancer hallmarks such as proliferation and migration, and metabolic and immune response reprogramming [4]. Therefore, combining RAS inhibitors with metabolic pathway inhibitors holds promise in clinical trials (Figure 1) (Boxes 1 and 2).

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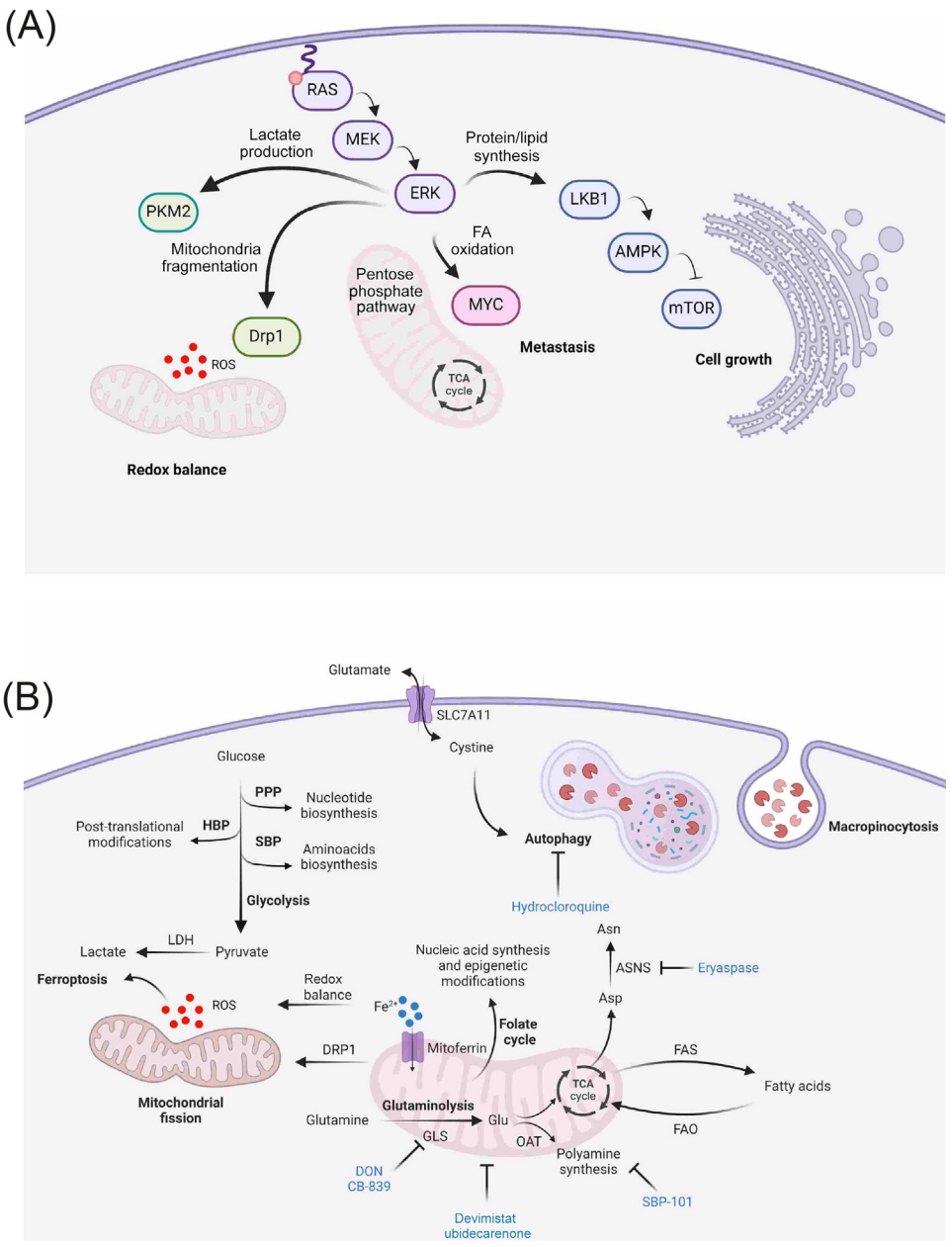

Figure 1. Targeting tumor metabolic pathways and key metabolic signaling molecules. (A) The RAS pathway regulates various cellular processes, including gene expression for proliferation and survival via the extracellular signal-regulated kinase (ERK) pathway. It also impacts metabolic pathways like the pentose phosphate pathway (PPP) and fatty acid metabolism. Mitochondrial dynamics, controlled by Dynamin-related protein 1 (DRP1), are influenced by RAS, affecting fragmentation. RAS intersects with mammalian target of rapamycin (mTOR), regulating protein and lipid synthesis. (B) Metabolic pathways such as the PPP, the hexosamine biosynthetic pathway (HBP), and the serine biosynthetic pathway (SBP) contribute to nucleotide synthesis and glycosylation. Glycolysis produces ATP, while glutaminolysis fuels the tricarboxylic acid (TCA) cycle. Polyamine synthesis is tightly regulated, and autophagy maintains homeostasis. The role of autophagy-mediated SLC7A11 regulation to modulate cysteine metabolism and intracellular cysteine pool supply is reported. Mitochondrial reactive oxygen species (ROS) production is balanced for signaling, while

(Figure legend continued at the bottom of the next page.)

Glossary

Aerobic glycolysis (Warburg effect): a metabolic process where cells use glycolysis even in the presence of oxygen.
Branched-chain amino acids (BCAAs): essential amino acids which include leucine, isoleucine, and valine.
Cancer-associated fibroblasts (CAFs): stromal cells in the tumor microenvironment associated with the production of extracellular matrix.
Cluster of differentiation (CD8) T cells: cytotoxic T cells that play a key role in immune responses against cancer.
Dendritic cells (DCs): antigen-presenting cells crucial for initiating adaptive immune responses.
Devimistat: a stable analog of lipoate, a catalytic intermediate used to alter mitochondrial metabolism in tumor cells. Investigated in clinical trials for metastatic pancreatic cancer.
6-Diazo-5-oxo-L-norleucine (DON): a broadly active glutamine antagonist with a two-step, mechanism-based mode of inhibition across multiple glutamine-utilizing enzymes. First DON binds to the glutamine active site, and then it irreversibly inhibits the enzyme by forming a covalent adduct.
Ferroptosis: a form of cell death involving iron-dependent lipid peroxidation.
FOLFIRINOX: a chemotherapy regimen combining oxaliplatin, leucovorin, irinotecan, and fluorouracil; it is often used in pancreatic cancer treatment.
Glutaminase synthase 1 (GLS1): a mitochondrial enzyme that catalyzes the production of glutamate from the amino acid glutamine, which then feeds into the TCA cycle.
Hexosamine biosynthetic pathway (HBP): a metabolic pathway for the biosynthesis of glycosylated products.
Hydroxychloroquine (HCQ): an autophagy inhibitor; it impedes the fusion of lysosomes to autophagosomes.
Mitochondrial oxidative phosphorylation: a process in which cells generate energy through the oxidation of nutrients.
Myeloid-derived suppressor cells (MDSCs): immunosuppressive cells derived from a myeloid lineage.
Natural killer (NK) cells: immune cells capable of killing tumor cells.
Ornithine aminotransferase (OAT): a key enzyme in polyamine synthesis,

Glucose metabolism

During tumor evolution, the acquired hypoxia fosters mutant *KRAS* and *TP53* PDAC cells to sustain their glucose avidity through different mechanisms, such as increased glucose uptake mediated by glucose transporter 1 (GLUT1), induction of glycolytic enzymes, and promotion of lactate production. Despite their preferential glycolytic phenotype, PDAC cells can promote **oxidative phosphorylation (OXPHOS)** as a compensatory mechanism [5,6] (Figure 2) to overcome the response to lactate dehydrogenase (LDH) targeting [7]. The simultaneous inhibition of KRAS effectors and the disruption of glycolysis highlights the importance of combining treatments that address both cancer metabolism and oncogenic signaling pathways.

The preferential use of glycolysis favors an anabolic state [8] (Figure 2), for *de novo* nucleotide biosynthesis (the **pentose phosphate pathway**, **PPP**) or for the synthesis of precursors for post-translational modifications (**hexosamine biosynthetic pathway**, **HBP**) [9].

Unlike the previous understanding, fatty acid β-oxidation (FAO) rather than glycolysis may provide energy maintenance to support PDAC [10] (Figure 1). Upregulation of enzymes that catalyze *de novo* fatty acid synthesis, such as fatty acid synthase (FASN), is linked with poor survival and decreased gemcitabine sensitivity [11].

Glutamine metabolism

Glutamine is the body's most abundant amino acid, serving as the primary source of nitrogen for amino acid and nucleotide biosynthesis, and as a source of carbon to replenish the **tricarboxylic acid (TCA) cycle** and fuel biosynthetic processes for PDAC growth [12]. Glutamine maintains redox balance through glutathione biosynthesis and generation of NADPH. Unlike normal cells, PDAC cells preferentially use glutamine-derived aspartate to produce NADPH equivalents through the malic cycle, and this represents a promising metabolic vulnerability [13] (Box 3).

Glutamine availability directly influences the mammalian target of rapamycin (mTOR) pathway, a master regulator of metabolic adaptation. This pathway is negatively regulated by PI(3,4)P2-dependent class II PI3K in response to glutamine deprivation in preclinical models of pancreatic cancer [14]. Despite the metabolic plasticity of cancer cells hindering the success of glutamine inhibitors as standalone agents, promising results have emerged from combining bis-2-(5-phenylacetamido-1,3,4-thiadiazol-2-yl)ethyl sulfide (BPTES), an inhibitor of **glutaminase synthase 1 (GLS1)** with everolimus (an mTOR inhibitor) in a subset of PDAC mouse models lacking expression of class II PI3K, PI3K-C2γ [14]. This suggests that stratifying tumors based on molecular characteristics may enhance the efficacy of glutamine inhibitors. However, the effectiveness of GLS1 inhibitors has been impeded by the activation of compensatory mechanisms. Alternatively, inhibitors with broader specificity, such as **6-diazo-5-oxo-L-norleucine (DON)**, are being explored to overcome these challenges [15]. DON is a broadly active glutamine antagonist that targets various glutamine-utilizing enzymes. To overcome side effects of broad range targeting, new formulations with better pharmacokinetic properties (i.e., orally available) are in development. DRP-104, a pro-drug version of DON, overcame DON-associated toxicity, and in combination with trametinib, it decreased PDAC growth and compensated extracellular signal-regulated kinase (ERK) overexpression [15]. The

converting arginine and ornithine into glutamate.
Oxidative phosphorylation (OXPHOS): an electron transfer chain driven by substrate oxidation that is coupled to the synthesis of ATP through an electrochemical transmembrane gradient.
Pentose phosphate pathway (PPP): a metabolic pathway generating ribose 5-phosphate for nucleotide biosynthesis.
RAS: a major protein, often mutated in PDAC, associated with metabolic rearrangements during cancer evolution.
Reactive oxygen species (ROS): chemically reactive molecules containing oxygen, often involved in cell signaling.
Tricarboxylic acid (TCA) cycle: also known as the Krebs cycle, it is the major energy-yielding metabolic pathway in cells.
Tumor-associated macrophages (TAMs): macrophages present in the tumor microenvironment.
Tumor immune microenvironment (TIME): the surroundings in which a tumor exists, including stromal cells, extracellular matrix, immune cells, and blood vessels.
Ubidecarenone (coenzyme Q10): an agent modulating mitochondrial function by influencing energy generation in cancer cells.

excessive ROS accumulation, due to cytosolic or mitochondrial events, can lead to ferroptosis. Cytosolic iron (Fe) crosses the inner mitochondrial membrane through the mitochondrial Fe importer, mitoferrin. DRP1-mediated mitochondrial fission is crucial for network health. Blue highlights indicate drugs targeting these metabolic pathways. Abbreviations: Asn, asparagine; ASNS, asparagine synthetase; Asp, aspartate; DON, 6-diazo-5-oxo-L-norleucine; FAO, fatty acid β-oxidation; FAS, fatty acid synthesis; Glu, glucose; GLS, glutaminase synthase; LDH, lactate dehydrogenase; OAT, ornithine aminotransferase. Figure created with BioRender.

Box 1. Metabolic heterogeneity

The high degree of complexity and heterogeneity of the metabolic profile of pancreatic cancer continues to pose a challenge to the effectiveness of existing treatments (see Table 1 in main text).

Metabolic heterogeneity is emerging as a key feature of PDAC, inspiring an alternative type of classification based on the bioenergetic preferences and the response to metabolic inhibitors, that also correlate with transcriptional subtypes: (i) glycolytic (quasimesenchymal transcriptional subtype), (ii) lipogenic (classical signature), and (iii) slowly proliferating [66]. These metabolic states can co-occur within the same tumor due to nutrient disparity between different regions and elements of the tumor mass. Cells with diverse metabolic processes coexist and mutually impact each other, generating a dynamic environment. Therapeutic options should take into consideration not only the metabolic vulnerabilities *per se*, but also the symbiotic support mechanism within different areas of the pancreas. For instance, cells located in hypoxic regions produce lactate, which can be utilized by PDAC cells situated in well-oxygenated areas [67]. In addition, PDAC cells with a constitutive active stress response support the mitochondrial metabolism of other PDAC cells with limited respiration [68]. Thus, the crosstalk between PDAC cells with different metabolic characteristics may interfere with metabolic-based treatment.

Metabolic heterogeneity is not only influenced by spatial organization, but also by the degree of evolution. During PDAC progression, the mitochondrial metabolism of pancreatic tumor-initiating cells is substituted by the glycolic profile of bulk tumors [69]. However, metastasis formation is characterized by the switch from anabolic glucose metabolism to oxidative PPP [70].

immunomodulatory effect of DON suggests that the targeting of metabolism in combination with immunomodulators could be effective.

Unlike other tumors, PDAC uses glutamine as a main source of ornithine, the starting point for the synthesis of polyamine [16] (Figure 1), a polycationic molecule whose expression is transcriptionally regulated by RAS and MYC and correlates with poor survival [17]. It is currently an open question whether polyamine deriving from different substrates could have different functions. One of the main polyamines involved in the PDAC immune landscape is spermine [18], whose analog is currently under clinical investigation (Table 1). The inhibition of **ornithine aminotransferase (OAT)**, which converts glutamate into ornithine, was sufficient to decrease tumor growth, while polyamine inhibitors as single agents had limited therapeutic success [19]. The combined inhibition of ornithine decarboxylase (ODC), which converts ornithine to putrescine, and polyamine transporters resulted in reduced PDAC cell proliferation [20] and overcame resistance to drugs already used in the clinic (such as erlotinib) [21].

Scavenging pathways

The impact of mitochondrial dynamics on the metabolic behavior of cancer cells is substantial, influencing cell transformation and tumor invasion (Figure 1). Mitochondrial fragmentation is linked to the promotion of cell transformation via ERK1/2-mediated phosphorylation of Dynamin-related protein 1 (Drp1) [22,23]. FAM49B, a 'tumor suppressor' protein, regulates oxidative stress, tumor proliferation, and invasion. PDAC biopsies negative for FAM49B, a regulator of mitochondrial function, correlated with a higher rate of lymph-node invasion [24]. Additional studies are required to comprehend the effects of oncogenic signaling pathways on mitochondrial dynamics.

Autophagy and RAS-mediated macropinocytosis work together to provide nutrients and sustain energy demand for PDAC growth (Figure 1). Upon inhibiting autophagy, PDAC cells upregulate nuclear factor erythroid 2-related factor 2 (NRF2)-mediated transcription of macropinocytosis pathway components, as a compensatory mechanism, suggesting that the combined inhibition of autophagy and macropinocytosis may be beneficial [25]. Among metabolic substrates provided by autophagy, ferritin is degraded in the lysosome (ferritinophagy) to release iron to sustain tumor progression [26]. Autophagy is also responsible for resistance to target therapies, such as ERK and MEK inhibitors, which increase the autophagic flux, suggesting that the combination with **hydroxychloroquine (HCQ)** would be beneficial (Table 1). Autophagy is not only critical

Box 2. Preclinical models of pancreatic cancer

Countless failures of targeted therapy in Phase 1/2 clinical trials partially reflect the inaccuracy of preclinical models that poorly recapitulate drug response and therapy resistance. The elevated heterogeneity, the complex intracellular and inter-organ interplay, and the influence of the microenvironment are key features that should be taken into consideration when choosing the experimental model. The main preclinical models used to test pancreatic cancer development and drug response are listed in the following sections.

Cell lines

Established cell lines derived from patient tumor samples and cultured in a plastic dish.

Main applications: cell-autonomous phenotypes, cell response to stimuli or drugs, cell growth measurements and other biological assays, genetic manipulation.

Advantages: unlimited supply of human cells, suitable for high-throughput studies at low costs.

Disadvantages: 2D growth on artificial substrates and *in vitro* selection of tumor cells cannot recapitulate the complexity of an organism.

Xenograft mouse models

Injection of patient-derived tumor (PDX) or of human cancer cells subcutaneously (heterotopic) or directly in the pancreas (orthotopic) of immunodeficient mice.

Main applications: rate of tumor growth, responsiveness to various drugs, and time to disease progression.

Advantages: influence of the totality of the body, guiding personal treatment supported by the solid consistency of clinical outcomes (PDX), and maintaining their genetic heterogeneity as well as the histological makeup of the patient and preserving them over the passages (PDX).

Disadvantages: non-physiological growth of the tumor that lacks its complex TIME, useless for immunotherapeutic studies.

Human PDAC organoids

3D cultures of dissociated primary pancreatic tissue propagated using a matrix and a tissue-specific medium [71,72].

Main applications: high-throughput drug screening.

Advantages: organoids show greater similarity with primary tumors compared with cell lines.

Disadvantages: limited use for immuno-oncology studies, despite efforts to generate co-culture organoids with other cell types (i.e., CAFs, pancreatic stellate cells, and immune cells).

Genetically engineered mouse (GEM) models

The GEM model LSL-KrasG12D/+; LSL-Trp53R172H/+; Pdx1-Cre (KPC) was the first model expressing key genetic drivers that induce the spontaneous formation of pancreatic tumors within a few months [73]. Clustered regularly interspaced short palindromic repeats (CRISPR)-mediated technology allowed integration of the 'gold standard' with novel conditional mouse models carrying KRAS mutations other than G12D [74].

Main applications: progression of invasive and metastatic disease and immunotherapy development.

Advantages: initiation and progression of pancreatic cancer in these mice closely mimics those in human disease, allowing clinically relevant evaluation of potential therapies or methods for early detection.

Disadvantages: high costs, long time necessary for the mouse to develop tumors, difficult to evaluate tumor mass dimensions, requiring sophisticated imaging techniques.

for providing energy but also for cysteine-dependent **reactive oxygen species (ROS)** detoxification to prevent cellular damage and **ferroptosis**-induced cell death [27,28]. The depletion of cysteine and the consequent promotion of ferroptosis inhibits PDAC growth in preclinical models, suggesting a promising translational impact of cysteine homeostasis into the clinics [28].

Box 3. Phosphoinositides and energy metabolism

Phosphoinositides are a family of minority signaling lipids that play a crucial role in a large number of cellular processes [75]. These phospholipids are integral components of cell membranes and act as molecular switches, orchestrating key biological signaling pathways, including cell proliferation, membrane trafficking, and cytoskeleton rearrangements [76]. Dynamic phosphorylation at various positions on the inositol ring, regulated by phosphoinositide kinases and phosphatases, allows phosphoinositides to regulate the activity of numerous enzymes and proteins involved in energy metabolism. Among their multifaceted functions, their significance in metabolic adaptation emerges as a critical aspect of cellular homeostasis. Phosphoinositides emerged as pivotal mediators orchestrating nutrient sensing in pancreatic cancer. A comprehensive exploration revealed their effects on metabolic processes, including glucose metabolism, amino acid uptake, and lipid synthesis [77]. This regulatory ability empowers pancreatic cancer cells to thrive resiliently within the challenging milieu of nutrient-deprived tumor microenvironment [78].

In the field of metabolic control, insulin, a key hormone, relies on the complex signaling coordination of phosphoinositides to carry out its regulatory functions. Phosphoinositides are integral constituents of the insulin signaling pathway, controlling the translocation of glucose transporters, fostering responsive glucose uptake in tandem with the ever-changing requirements of cellular energy. In pancreatic cancer cells, phosphoinositides act as crucial contributors to their adaptive repertoire, constantly adjusting to the fluctuations of nutrient availability and energy status [14]. These lipids modulate the activity of energy-sensing kinases, exemplified by the pivotal roles played by AMP-activated protein kinase (AMPK) and mTOR in regulating cellular energy homeostasis. Furthermore, within the context of lipid metabolism, phosphoinositides are key players in the regulation of the enzymatic processes governing lipid synthesis, breakdown, and storage [79]. The dynamic interplay between phosphoinositides and lipid metabolism is a cornerstone in maintaining membrane integrity and generating bioactive lipid signaling molecules. In the sphere of autophagy, the cellular mechanism dedicated to the catabolism and recycling of cellular components, phosphoinositides coordinate the formation of autophagosomes, essential structures tasked with sequestering cellular materials for subsequent degradation [80]. This regulatory process of phosphoinositides plays a pivotal role in shaping cellular adaptation to nutrient stress. In sum, the regulatory influence of phosphoinositides extends across nutrient sensing, insulin signaling, energy dynamics, lipid metabolism, and autophagy, showing a comprehensive portrait of their essential roles in cellular homeostasis.

Metabolic changes in the TIME

The tumor microenvironment (TME) in PDAC is heterogeneous and characterized by a desmoplastic stroma containing various cell types, such as **cancer-associated fibroblasts (CAFs)**, endothelial and lymphatic cells, pericytes, neuronal cells, and immune cells. This environment, often referred to as TIME (TME with emphasis on the immune system), includes myeloid cells such as **tumor-associated macrophages (TAMs)**, **myeloid-derived suppressor cells (MDSCs)**, neutrophils, and **dendritic cells (DCs)**, as well as T and B cells, and **natural killer (NK) cells**. Interactions among these cells – along with cytokines, chemokines, and growth factors – add complexity to the ecosystem. All cells in the stroma, including tumor cells, are influenced by metabolic changes and compete for nutrients and glucose, impacting their energy production. However, the precise adaptation of pancreatic TIME to metabolic perturbations remains unclear. Tumor cells can reprogram their metabolism to support growth and create a hostile environment that suppresses antitumor responses.

Hypoxia and glucose metabolism

Dysfunctional and immature blood vessels foster hypoxic cells to switch toward non-oxidative pathways and anaplerotic metabolism to grow (Figure 2). Unlike innate and adaptive effector cells that depend on **aerobic glycolysis (Warburg effect)**, naive or memory T cells, as resting cells, commonly rely on catabolic metabolism, including OXPHOS and FAO to support their survival [29], similarly to the alternative activated (M2) macrophages. Classical activated macrophages (M1) are instead characterized by activation of the PPP following glycolysis [30]. Tumor cells adapt their metabolism to the hypoxic environment, which dampens the effector functions of immunosurveillance. For example, in PDAC, hypoxia inhibits the cytolytic activity of NK cells by reducing the expression of miR-1275, which correlates with the production of perforin, interferon γ (IFNγ) and tumor necrosis factor α (TNFα) [31]. It is well known that hypoxia induces the stabilization of hypoxia-inducible factors (HIFs) 1 and 2, which correlates with chemoresistance

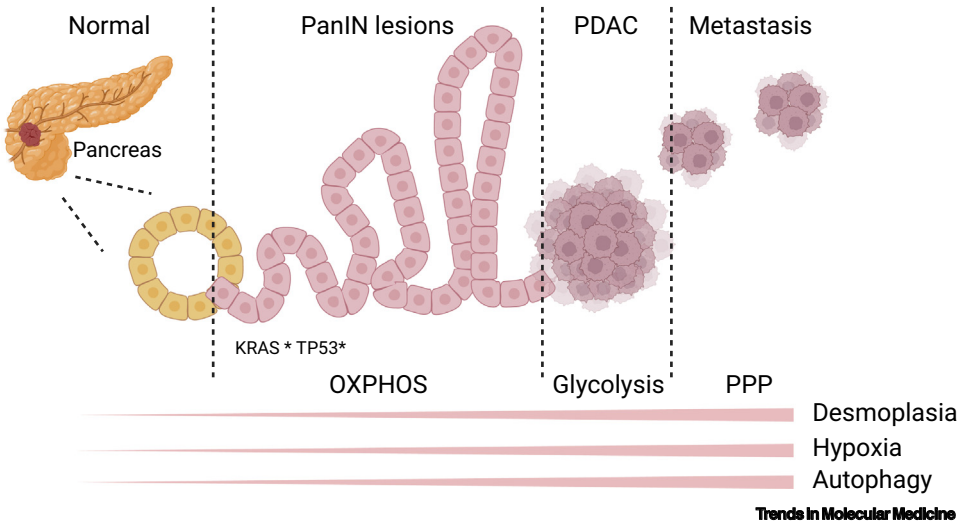

Figure 2. Pancreatic cancer pathogenesis and metabolic reprogramming. The pathogenesis of pancreatic cancer involves a complex series of events. Initially, genetic mutations, such as alterations in KRAS and TP53 genes, may occur, leading to the initiation of pancreatic intraepithelial neoplasia (PanIN). In the early stages, tumor cells predominantly rely on cellular respiration (oxidative phosphorylation, OXPHOS). However, as the disease progresses, there is a shift in metabolic preferences. In advanced stages, pancreatic cancer cells adopt a glycolytic phenotype characterized by heightened glucose uptake and lactate production. Ultimately, metastatic tumor cells activate the pentose phosphate pathway (PPP) to support increased nucleotide synthesis and combat oxidative stress. These metabolic changes, accompanied by the dysregulation of key signaling pathways, contribute to the aggressive nature of pancreatic ductal adenocarcinoma (PDAC). The tumor immune microenvironment, characterized by desmoplasia and consequent increase of hypoxia and autophagy levels, further influences disease progression and treatment resistance. Figure created with BioRender.

[32] and metastasization [33]. The depletion of HIF2, but not HIF1, in CAFs improved PDAC survival in mice by limiting and impairing M2 and regulatory T cell recruitment into the tumor, without affecting fibrosis [34]. HIF2 is also responsible for the accumulation of innate lymphoid cells (ILCs), which assume a regulatory/suppressive profile with the secretion of the anti-inflammatory IL10 when in hypoxic environment [35].

Glutamine addiction

Cancer proliferation and immune cell activation are sustained by glutaminolysis [32,36] (Figure 2). In PDAC, glutamine deprivation increases antitumor responses by both innate and adaptive cells. Macrophages are more active in phagocytosis of tumor cells in deprivation of linker for activation of T cells family member 2 (LAT2), a transporter of glutamine and leucine, increasing their effect in the presence of chemotherapy-treated tumor cells and the depletion of macrophage-derived IL18. Under these conditions, tumor cells express less CD47, the 'do not eat me' ligand, representing an 'easy target' for phagocytes, and especially M1 macrophages [37]. However, α-ketoglutarate, produced by glutamine metabolism, favors the M2 polarization and activation, with higher expression and activity of arginase-1, and suppresses the nuclear factor κB (NF-κB) pathway in M1, which induces the expression of proinflammatory cytokines such as IL1b, TNFα, IL6, and IL12 [38]. In line with the crucial role of cytokines in modulating TIME metabolism, the absence of the proinflammatory cytokine IL17A affects macrophage polarization and metabolism, leading to the up-modulation of M1 typical markers but also OXPHOS and FAO, with the consequence of rendering macrophages dispersed in the tumor mass less greedy of and dependent on glucose [39]. Even T cells are actively recruited into the tumor and are more prone in their antitumor functions, such as cytokine secretion, when glutamine metabolism is blocked. Indeed, IFNγ downregulates the expression of

Table 1. Representative clinical trials regarding metabolic targeting in pancreatic cancer

NCT number	Status	Phase	Therapy	Target
NCT01835041[i]	Completed	1	Devimistat[a] + FOLFIRINOX[b]	Mitochondrial function
NCT05733000[ii]	Recruiting	2	Devimistat + HCQ and 5-FU[c]/gem	Mitochondrial function
NCT02650804[iii]	Completed	2	Ubidecarenone[d] + gem	Mitochondrial function
NCT03665441[iv]	Completed	3	Eryaspase[e] + gem/nab-pacl or irinotecan[f]/5-FU	Asparaginase
NCT01978184[vi]	Completed	2	HCQ[g] + gem and nab-pacl[h]	Autophagy
NCT04386057[vii]	Active	2	HQC + temuterkib[i]	Autophagy
NCT03825289[viii]	Recruiting	1	HCQ + trametinib[j]	Autophagy
NCT04132505[ix]	Recruiting	1	HCQ + binimetinib[k]	Autophagy
NCT03412799[x]	Completed	1	Gemcitabine[l] and nab-paclitaxel with or without SBP-101	Polyamine synthesis
NCT05254171[xi]	Recruiting	3	Gemcitabine and nab-paclitaxel with or without SBP-101	Polyamine synthesis
NCT03006302[xii]	Active	2	Epacadostat, pembrolizumab, and CRS-207, with or without cyclophosphamide/GVAX	IDO1[m] inhibitor combined with immunotherapy

[a]Devimistat (CPI-613): inhibitor of the mitochondrial enzyme pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase.
[b]FOLFIRINOX: chemotherapy combination that contains leucovorin calcium (folinic acid), fluorouracil, irinotecan hydrochloride, and oxaliplatin.
[c]5-FU (fluoropyrimidine 5-fluorouracil): inhibition of thymidylate synthase (TS) and incorporation of its metabolites into RNA and DNA.
[d]Ubidecarenone (coenzyme Q10): essential cofactor in mitochondrial oxidative phosphorylation.
[e]Eryaspase: L-asparaginase (hydrolyzes and reduces asparagine levels in plasma) encapsulated in red blood cells.
[f]Irinotecan: inhibits the action of topoisomerase I, causing double-strand DNA breakage.
[g]HCQ (hydroxychloroquine): interfere with lysosomal activity and autophagy.
[h]nab-pacl (abraxane): combines the chemotherapy drug paclitaxel (anti-microtubule drug) with albumin.
[i]Temuterkib (LY3214996): ERK1/2 inhibitor.
[j]Trametinib (GSK1120212): MEK1/2 inhibitor.
[k]Binimetinib (MEK162): MEK1/2 inhibitor.
[l]Gemcitabine: an analog of deoxycytidine which inhibits DNA synthesis.
[m]IDO1: indoleamine 2,3-dioxygenase 1.

SLC3A2 and SLC7A11, both involved in the antiporter system of glutamate and cystine, and impairs the uptake of cystine by tumor cells. Consequently, the oxidative stress and lipid peroxidation in tumor cells lead to ferroptosis and antitumor response [40].

BCAAs and nutrients

The intracellular accumulation of **BCAAs** enhances **cluster of differentiation (CD8) T cell** effector and memory functions by inducing GLUT1 expression and glucose metabolism through glycolysis and the TCA cycle [41]. Single-cell RNA sequencing (scRNA-seq) analysis revealed an enrichment of activation and memory-like signature, high proportions of specific $CD8^+$ T cell markers, and a down-modulation of the exhausted marker TOX in the spleen of genetically engineered mouse (GEM) models characterized by significant BCAA accumulation [41]. Additionally, the catabolism of BCAAs was shown to be crucial for the development and progression of PDAC, and a low-BCAA diet dampened PDAC progression [42]. Fasting or fasting-mimicking diets increased resistance to DNA damage in normal cells but sensitized cancer cells, particularly those with limited autophagy, promoting aging [43]. Fasting also has anti-inflammatory effects, while metabolic overload coincides with inflammation and decreased cancer immunosurveillance [44]. Furthermore, obese individuals show more differentiated CD8 T cells and impaired DCs,

which are crucial in tumor antigen recognition and killing [45,46]. In PDAC, the low expression of major histocompatibility complex I (MHC-I) molecules induced by autophagy hinders effector CD8 T cells from exerting their killing function, but inhibition of autophagy increased MHC-I molecule expression and the T cell-mediated antitumor response [47]. Therefore, autophagy inhibition could be combined with immune checkpoint blockade to sustain the effector recognition of tumor cells by CD8 T cells.

Overall, metabolic targeting can reprogram the TIME and overcome immunotherapy resistance or tolerance. For instance, inhibiting LDH reduces lactate production, enhancing the antitumor activity of CD8 T cells [48]. Additionally, inhibiting glutaminolysis shifts the immune response from Th17 to Th1, counteracting the protumoral effects of Th17 [49]. However, this approach may lead to T cell exhaustion, suggesting potential combination with immune checkpoint treatments to boost T cell effector activity.

Clinical trials based on antimetabolic drugs

Thus far, the accumulated results from clinical trials exploiting metabolic modulation in pancreatic cancer have generally yielded, at most, only modest clinical benefits (Figure 1 and Table 1). Over the past decade, a significant proportion of the scientific efforts to translate the metabolic reprograming concept into the clinic have been based on old drugs with very complex metabolic functions, such as statins, metformin, ascorbic acid, fish oil, to name a few [50]. A multitude of new clinical trials are underway using novel drugs designed to disrupt targeted metabolic dependencies in PDAC. One such agent used to alter the mitochondrial metabolism, **devimistat**, is a stable analog of a lipoate catalytic intermediate selectively targeting mitochondrial enzyme activities and redox status, leading to apoptosis, necrosis, and autophagy of tumor cells [51] (Figure 1). Devimistat was investigated in a Phase 1 open-label dose-escalation clinical trial in combination with modified **FOLFIRINOX** (oxaliplatin, leucovorin, irinotecan, and fluorouracil) in patients with metastatic pancreatic cancer (NCT01835041[i]). The combination was well tolerated, with a toxicity profile like the historical data reported in the PRODIGE trial of FOLFIRINOX [52]. The maximum tolerated dose (MTD) of devimistat was 500 mg/m^2. Of the 18 patients given the MTD, 11 (61%) achieved an objective response, which is higher than the historical data with FOLFIRINOX alone, suggesting an encouraging signal for synergy with this combination [53]. A Phase 2 open-label multi-cohort clinical trial with devimistat in combination with HCQ and fluorouracil or gemcitabine in pancreatic cancer is currently recruiting patients (NCT05733000[ii]). **Ubidecarenone (coenzyme Q10)** is another agent which modulates mitochondrial function by switching cancer energy generation from glycolysis to **mitochondrial oxidative phosphorylation** to generate ROS and activate apoptosis [54] (Figure 2). A Phase 2 open-label, non-randomized clinical trial evaluated ubidecarenone in combination with gemcitabine in heavily pretreated metastatic pancreatic cancer (NCT02650804[iii]). While the final results are not yet available, the preliminary report showed that the drug was well tolerated and among the 18 evaluable patients, nine (50%) achieved stable disease as the best response, while the historical stable disease ratio expected for gemcitabine monotherapy ranges from 28% to 41.5% in the first-line setting [52,55]. Constitutive KRAS activation, which is almost uniformly present in PDAC, promotes metabolic dysregulation leading to addictions to metabolites such as asparagine and glutamine [13,56]. Asparagine synthetase (ASNS) catalyzes the synthesis of asparagine from aspartate and glutamine, while asparaginase (ASNase) hydrolyzes serum asparagine, thereby starving ASNS-deficient cells, which is observed in most cases of PDAC [57]. A Phase 2b open-label randomized trial assessed the efficacy and safety of encapsulated ASNase within erythrocytes (eryaspase) as second-line therapy in combination with either gemcitabine or FOLFOX (oxaliplatin, leucovorin, and fluorouracil) in advanced PDAC [58]. The combination of eryaspase and chemotherapy was well tolerated and associated with improvements in overall

survival (OS) and progression-free survival (PFS), irrespective of ASNS expression level [58], raising hopes of a new treatment option for patients with PDAC. However, overexpression of ASNS in CD8 T cells seems to help maintain their effector antitumoral functions [29]. The subsequent Phase 3 open-label, multicenter, randomized Trybeca-1 trial enrolled 512 subjects to receive a second-line regimen of gemcitabine/nab-paclitaxel or irinotecan/fluorouracil with or without eryaspase (NCT03665441[iv]). Disappointingly, the study did not meet the primary endpoint, with median OS for patients treated with eryaspase plus chemotherapy of 7.5 months compared to 6.7 months for chemotherapy alone (HR 0.92, 95% CI 0.76–1.11, $P = 0.375$). There was a trend for OS benefit in the 107 patients treated with eryaspase and irinotecan/fluorouracil compared with 109 patients in the control subgroup, with a median OS of 8.0 versus 5.7 months, respectively (HR 0.81, 95% CI 0.60–1.09). Like asparagine, glutamine is a vital metabolite for pancreatic cancer, serving as a critical source of carbon and nitrogen to fuel tumor progression. Previous clinical efforts using the glutamine antagonist DON were halted due to adverse effects [59]. DRP-104 is a novel prodrug of DON that is activated in the TME, which may be advantageous by limiting side effects, but it is not yet in clinical development for PDAC. CB-839, also known as telaglenastat, is a potent inhibitor of glutaminase 1, and has been studied in a Phase 1 open-label, dose escalation and expansion clinical trial in solid tumors but yielded limited clinical effects (NCT03875313[v]). Notably, preclinical studies with CB-839 showed that, despite marked initial growth inhibition, pancreatic cancer cells develop rapid adaptive metabolic rewiring to overcome initial glutamine dependency, and that combinatorial metabolic inhibition may be required to yield clinical benefits for patients [60].

The strong oncogenic addiction to KRAS signaling seen in PDAC also induces increased autophagy. Inhibition of autophagy can be attained with HCQ, which impedes the fusion of lysosomes to autophagosomes [61]. To assess the clinical impact of autophagy inhibition in PDAC, a Phase 2 randomized clinical trial was conducted to determine whether HCQ improves OS in combination with gemcitabine and nab-paclitaxel in the metastatic setting. In total, 112 patients were enrolled, 55 to receive gemcitabine and nab-paclitaxel plus HCQ, and 57 in the control arm to receive chemotherapy alone. Unfortunately, the OS at 12 months was 41% (95% CI 27–53) in the HCQ group and 49% (95% CI 35–61) in the control group (NCT01978184[vi]). Most recent efforts to target autophagy in PDAC have been centered on the co-inhibition of the mitogen-activated protein kinase (MAPK) pathway, which has been shown to decrease glycolysis and mitochondrial function in *in vitro* models [62]. Indeed, combining MEK or ERK inhibitors with HCQ leads to marked regression of PDAC models *in vivo* [63,64], including an exciting report of a patient with metastatic PDAC treated with trametinib plus HCQ resulting in a partial response [63]. Given these encouraging translational and clinical results, several early-phase clinical trials are currently ongoing to understand whether the combined approach of MEK or ERK blockade with autophagy inhibition with HCQ provides clinical benefit to patients with PDAC (NCT04386057[vii], NCT03825289[viii], and NCT04132505[ix]). The modulation of polyamine metabolism is another promising approach under clinical development in PDAC. A Phase 1 open-label clinical trial evaluated the polyamine analog SBP-101 in combination with standard-of-care gemcitabine and nab-paclitaxel (NCT03412799[x]). Treatment was relatively well tolerated but some patients experienced serious hepatic and retinal toxicity, which occurred after prolonged treatment and required dose reduction or discontinuation [65]. These events warrant attention for the future clinical development of SBP-101. Importantly, the regimen showed preliminary signs of efficacy. At the recommended dose and schedule, 43% of patients achieved a partial response and 39% experienced stable disease, comparing very favorably with historical data of gemcitabine and nab-paclitaxel alone [55]. The ASPIRE trial is a large double-blind, placebo-controlled Phase 3 study that is currently enrolling patients with PDAC to receive gemcitabine and nab-paclitaxel with or without SBP-101 in the first-line setting (NCT05254171[xi]). The immunosuppressive

Clinician's corner

Over the past decade, numerous clinical trials exploiting metabolic modulation in pancreatic cancer have generally failed to improve patients' outcomes. These shortcomings can be attributed at least in part to the use of old drugs with very complex metabolic functions, such as metformin and statins, as well as incomplete understanding of the critical metabolic hubs of pancreatic cancer.

The metabolic heterogeneity observed in human pancreatic cancers – driven by the interplay of glycolytic, lipogenic, and slowly proliferating states – represents a challenge to translate new therapeutic discoveries into clinical practice.

Several new clinical trials using novel drugs designed to disrupt targeted metabolic dependencies are ongoing. In some studies, rational combinations with chemotherapies or immunotherapies have been carefully devised. This approach may induce additional tumor-killing effects, without compounding toxicity, given that side effect profiles of metabolic modulators are generally non-overlapping with those from chemotherapies and immunotherapies.

Noteworthy therapeutic developments involve co-targeting of the MAPK pathway by blocking MEK or ERK kinases with autophagy inhibitors. In addition, the host of novel KRAS inhibitors that are currently under rapid clinical development may open a new frontier in the co-inhibition of MAPK and autophagy.

The results of later-phase studies such as the Phase 2 trial with IDO1 inhibitor combined with immunotherapies (NCT03006302[xii]) and the Phase 3 ASPIRE trial with the polyamine analog SBP-101 in combination with chemotherapy (NCT03412799[x]) are eagerly awaited. Positive results from these studies will have a major impact in clinical care and will power progress in the cancer metabolism landscape.

PDAC microenvironment is emerging as a new frontier for targeting metabolic dependencies. An ongoing Phase 2 open-label clinical trial is investigating epacadostat, an inhibitor of indoleamine 2,3-dioxygenase 1 (IDO1), in combination with pembrolizumab and CRS-207, with or without cyclophosphamide/GVAX in metastatic PDAC (NCT03006302[xii]). It will be noteworthy to understand whether impairing metabolic adaptation of PDAC enhances the clinical efficacy of immunotherapy in this recalcitrant disease.

Concluding remarks

This review underscores the critical role of metabolic reprogramming in the pathogenesis and progression of PDAC. The intricate metabolic heterogeneity observed within PDAC tumors, driven by the interplay of glycolytic, lipogenic, and slowly proliferating states, presents a formidable challenge in the quest for effective therapeutic strategies (see Outstanding questions). The symbiotic support mechanisms and crosstalk between cells with diverse metabolic characteristics further complicate the landscape, emphasizing the need for comprehensive and personalized approaches to treatment. While current research has shed light on potential therapeutic targets, such as inhibitors of RAS and glycolysis, clinical trials based on antimetabolic drugs are faced with ongoing challenges (see Clinician's corner). The exploration of novel agents like devimistat, ubidecarenone, and eryaspase showcases promising avenues, yet their efficacy and broader applicability demand rigorous investigation. The limitations in targeting specific metabolic pathways, the influence of TME heterogeneity, and the intricacies of the immune response underscore the complexity of PDAC. Future research should focus on unraveling these complexities, exploring combination therapies, and identifying robust biomarkers for patient stratification. Despite these challenges, the evolving landscape of metabolic research in PDAC offers optimism for innovative approaches, fostering a deeper understanding that holds the potential to transform the clinical management of this devastating disease. The journey towards conquering PDAC demands continued collaboration and a commitment to addressing the unresolved questions, ultimately bringing us closer to more effective and personalized therapeutic interventions.

Outstanding questions

How can the classification of pancreatic cancer based on bioenergetic preferences and metabolic responses be refined?

How can the spatial and temporal metabolic heterogeneity within pancreatic tumors be better characterized to guide more precise therapeutic interventions?

How can the role of mitochondrial dynamics in pancreatic cancer, influenced by oncogenic KRAS signaling, be further elucidated to explore its potential as a therapeutic target?

What are the underlying mechanisms and consequences of the interplay between autophagy and Ras-mediated micropinocytosis in sustaining nutrient supply for pancreatic cancer growth?

What are the specific immunomodulatory effects of glutamine inhibitors and their potential synergy with immunomodulators in the context of pancreatic cancer treatment?

What are the specific metabolic adaptations and perturbations in the pancreatic TIME in response to metabolic changes, and how do these adaptations impact the efficiency of antitumor responses?

How can metabolic targeting strategies be used to reprogram the pancreatic TIME and overcome immunotherapy resistance or tolerance, considering the diverse effects on different immune cell populations?

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT 3.5 tool to improve the quality of their scientific writing. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Resources

[i]https://clinicaltrials.gov/study/NCT01835041

[ii]https://clinicaltrials.gov/study/NCT05733000

[iii]https://clinicaltrials.gov/study/NCT02650804

[iv]https://clinicaltrials.gov/study/NCT03665441

[v]https://clinicaltrials.gov/study/NCT03875313

[vi]https://clinicaltrials.gov/study/NCT01978184
[vii]https://clinicaltrials.gov/study/NCT04386057
[viii]https://clinicaltrials.gov/study/NCT03825289
[ix]https://clinicaltrials.gov/study/NCT04132505
[x]https://clinicaltrials.gov/study/NCT03412799
[xi]https://clinicaltrials.gov/study/NCT05254171
[xii]https://clinicaltrials.gov/study/NCT03006302

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