Review

MOLECULAR METABOLISM

Metabolic plasticity in pancreatic cancer: The mitochondrial connection

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ABSTRACT

Background: Cellular metabolism plays a pivotal role in the development and progression of pancreatic ductal adenocarcinoma (PDAC), with dysregulated metabolic pathways contributing to tumorigenesis and therapeutic resistance. Distinct metabolic heterogeneity in pancreatic cancer significantly impacts patient prognosis, as variations in metabolic profiles influence tumor behavior and treatment responses.
Scope of the Review: This review explores the intricate interplay between mitochondrial dynamics, mitophagy, and cellular metabolism in PDAC. We discuss the significance of mitophagy dysregulation in PDAC pathogenesis, emphasizing its influence on treatment responses and prognosis. Furthermore, we analyze the impact of mitochondrial dynamics alterations, including fission and fusion processes, on PDAC progression and tumorigenesis.
Major Conclusion: Targeting mitochondrial metabolism holds promise for advancing PDAC therapeutics. Ongoing clinical trials underscore the therapeutic potential of modulating key regulators of mitochondrial dynamics and mitophagy. Despite inherent challenges, these approaches offer diverse strategies to enhance treatment efficacy and improve patient outcomes.

Keywords Pancreatic cancer; Mitochondria; Metabolism; Oxidative phosphorylation; Mitophagy

1. OVERVIEW ON PANCREATIC CANCER METABOLISM

Pancreatic ductal adenocarcinoma (PDAC) poses significant challenges due to its hidden onset, high malignancy, and the lack of effective treatments [1]. Together with surgery, adjuvant or neoadjuvant chemotherapy remains the primary treatment for patients with resectable or borderline resectable disease [2]. However, the extensive metabolic reprogramming exhibited by pancreatic cancer cells [3]interacts with oncogenes to affect the expression of key enzymes and signaling pathways, resulting in limited response to therapy and chemoresistance [3].
Metabolic reprogramming is recognized as a hallmark of cancer, driving the adaptation of malignant cells to their microenvironment [4]. While the metabolic phenotype of PDAC cells has historically been associated with an increased reliance on aerobic glycolysis, commonly referred to as the Warburg effect, this view has evolved. Recent evidence suggests that the Warburg effect reflects a disproportionate production of lactate despite sufficient oxygen availability and concurrent mitochondrial activity, rather than a strict preference for glycolysis over oxidative phosphorylation (OXPHOS) [5–7]. This energy metabolism rewiring allows cancer cells to generate ATP rapidly, while the diversion of glycolysis towards the biosynthetic pathways, provides the necessary building blocks for sustained cell proliferation and tumor growth [8]. Moreover, aerobic glycolysis drives extracellular acidosis and lactate accumulation, which contribute to shape the tumor microenvironment and cancer aggressiveness, by altering immune cell infiltration and other tumor microenvironment (TME) dynamics [9,10]. These factors, in turn, modulate the metastatic potential of PDAC cells and enhance their resistance to therapies. Indeed, many PDAC cells exhibit robust mitochondrial function, with OXPHOS playing a complementary role in energy production and biosynthesis. This metabolic plasticity underscores the importance of mitochondria in supporting tumor progression and therapeutic resistance [11,12].
Additionally, recent studies have highlighted the intricate interplay between mitochondrial metabolism and various signaling pathways involved in PDAC pathogenesis. Dysregulation of mitochondrial function, particularly within the context of the electron transport chain (ETC) and the tricarboxylic acid (TCA) cycle, emerges as a crucial determinant of tumor progression and therapeutic response [13]. Additionally, emerging evidence has demonstrated that PDAC cells are capable of

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Abbreviations: CSC, Cancer stem cell; ETC, Electron transport chain; FAO, Fatty acid oxidation; GLS, Glutaminase; Glu, Glutamate; Gln, Glutamine; GSH, Glutathione; GOT1, Aspartate Aminotransferase; GOT2, Aspartate Transaminase; HIF1α, Hypoxia-inducible factor 1-α; IDH1, Isocitrate dehydrogenase; IPMN, Intraductal Papillary Mucinous Neoplasm; MMP, Mitochondrial Membrane Potential; Mfn, Mitofusin; MitoMet, Mitochondria-targeted Metformin; Mito-Q, Mitoquinone; OCR, Oxygen consumption rate; OXPHOS, Oxidative phosphorylation; PDAC, Pancreatic Ductal Adenocarcinoma; ROS, Reactive Oxygen Species; TCA cycle, Tricarboxylic Acid Cycle; UCP2, Uncoupling protein 2

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dynamically modulating their metabolic pathways in response to stress [14]. Inhibition of glycolysis has been shown to enhance mitochondrial activity, upregulating enzymes involved in the TCA cycle and the ETC [15]. This compensatory shift further highlights the critical role of mitochondria in maintaining tumor cell viability under metabolic stress [6,14]. Notably, inhibition of glycolysis has been shown to upregulate the expression of enzymes involved in the TCA cycle and ETC, highlighting the compensatory role of mitochondrial OXPHOS in sustaining cell viability under metabolic stress [15]. For instance, recent studies have highlighted that mitochondrial activity in PDAC is finely tuned to balance ATP production and biosynthetic demands, with distinct subpopulations of cancer cells exhibiting variable OXPHOS rates that correlate with aggressiveness and prognosis [5,16]. Furthermore, alterations in lipid metabolism, particularly fatty acid oxidation (FAO), have gained attention as critical contributors to PDAC pathophysiology. Fatty acids serve as essential substrates for energy production and membrane biosynthesis in cancer cells, and dysregulated FAO has been implicated in tumor progression and chemoresistance [17]. Hypoxia, a common feature of the tumor microenvironment, exacerbates metabolic reprogramming by suppressing FAO and promoting a glycolytic phenotype through the activation of hypoxia-inducible factors (HIFs) [18]. Notably, intraductal papillary mucinous neoplasm (IPMN), a precursor lesion of PDAC, relies on FAO-mediated OXPHOS to sustain stemness properties, highlighting the significance of lipid metabolism in early pancreatic tumorigenesis [19].

Moreover, glutamine (Gln), one of the most abundant amino acid in the body, emerges as a key player in PDAC metabolism, serving as a versatile substrate for bioenergetic and biosynthetic pathways. Gln metabolism, or glutaminolysis, occurs predominantly within mitochondria and fuels the TCA cycle, providing intermediates for macromolecule synthesis and maintaining redox homeostasis [20]. Importantly, Gln addiction is a hallmark of PDAC, with cancer cells exhibiting elevated expression of Gln transporters to meet their metabolic demands [21]. The role of Gln in PDAC extends beyond energy production, as it also contributes to chemoresistance through the modulation of redox signaling and nucleotide synthesis [22].

Furthermore, mitochondrial dynamics and quality control mechanisms, such as mitophagy, play crucial roles in maintaining cellular homeostasis and regulating tumor progression. Dysregulated mitophagy has been implicated in PDAC pathogenesis, with aberrant mitochondrial turnover contributing to tumor growth and therapeutic resistance [23]. Notably, targeting mitochondrial dynamics represents a promising therapeutic strategy in PDAC, with emerging evidence highlighting the potential of mitophagy inhibitors and modulators to enhance the efficacy of conventional chemotherapeutics.

Pancreatic cancer remains a formidable challenge in oncology due to its aggressive nature and resistance to conventional therapies. Targeting mitochondrial metabolism has emerged as a promising therapeutic strategy in PDAC, with several agents under investigation to exploit vulnerabilities in mitochondrial function for therapeutic benefit. This review aims to summarize the current understanding of pancreatic cancer metabolism, focusing on the challenges posed by mitochondrial dysfunction and the potential clinical implications of targeting mitochondrial metabolism in PDAC.

2. MITOCHONDRIA AS CENTRAL ORCHESTRATORS OF CELLULAR METABOLISM

Cellular metabolism plays a critical role in tumor formation and progression, and its dysregulation is identified as a hallmark of cancer [24]. Specifically, many cancer cells exhibit a metabolic shift known as the Warburg effect, characterized by increased aerobic glycolysis for ATP production, even in the presence of oxygen, although this is not a universal feature across all cancers [25]. This metabolic reprogramming results in elevated glucose uptake, lactate production, and augmented Gln utilization within the TCA cycle. Gln serves as a substrate for oxidative catabolism within the TCA cycle, providing energy and building blocks for macromolecular synthesis. Alternatively, Gln can be reduced to maintain redox homeostasis through the production of NADPH and glutathione (GSH) [25]. In addition to ATP generation, mitochondria play vital roles in biosynthesis, redox balance, and waste elimination [26]. Recent scientific endeavors focus on unraveling the involvement of mitochondria in the rewiring of cellular metabolism during cancer development and progression.

2.1. Interplay between ETC and TCA cycle in cellular metabolism

Cells have two main mechanisms for energy production: glycolysis and mitochondrial OXPHOS (Figure 1). While many cancer cells preferentially rely on glycolysis even in the presence of oxygen, ATP production through OXPHOS remains important in certain contexts, especially when glycolysis is inhibited, suggesting metabolic plasticity in PDAC cell metabolism [27]. In PDAC cells, inhibition of glycolysis leads to the upregulation of various enzymes involved in the TCA cycle and the ETC [28]. Furthermore, inhibiting glycolysis renders PDAC cells more sensitive to inhibition of complex I and V, confirming the significance of OXPHOS for cell survival [28]. Both galactose-mediated glycolytic inhibition and low-glucose conditions resulted in increased mitochondrial membrane potential (MMP) and accelerated oxygen consumption rate (OCR) in PDAC cells, without affecting the overall mitochondrial count [28].

A recent study demonstrated the metabolic heterogeneity of PDAC cell lines, as evidenced by varying levels of basal respiration, mitochondrial ATP production, and respiratory spare capacity [27]. Differences in basal glycolysis and glycolytic reserve allow the classification of PDAC cell lines by basal energetic characteristics, which can also apply to patient-derived cells from the PaCaOmics program [27]. While this classification does not correlate with proliferative rate, it reveals a trend between patient survival and OXPHOS rate. Specifically, patients with high OXPHOS rates tended to have lower overall survival, although the difference is not statistically significant, likely due to the limited number of patients included in the analysis [27]. However, the difference becomes significant when considering the correlation between complex I expression (specifically, NADH:ubiquinone oxidoreductase subunit B8) and survival rate. Higher expression of complex I, which is more abundant in the high OXPHOS group, is associated with a lower survival rate [27]. Inhibiting complex I using phenformin sensitizes high OXPHOS PDAC cells to gemcitabine treatment both *in vitro* and *in vivo*. Particularly, the combined inhibition of OXPHOS and gemcitabine demonstrates beneficial anti-cancer effects in *in vivo* orthotopic mouse models, independent of the host immune system [27]. Furthermore, considering that the expression of mitochondrial respiratory genes correlates with high OXPHOS rates, transcriptomic analysis holds promise as a valuable tool for identifying high OXPHOS PDAC patients in clinical settings [27].

2.2. β-oxidation

β-Oxidation, a process primarily occurring in mitochondria, also involves peroxisomes as key players in the metabolism of fatty acids [29]. Both organelles work together to break down long-chain fatty acids, with peroxisomes initially handling the oxidation of very long-chain fatty acids and branched-chain fatty acids before transferring

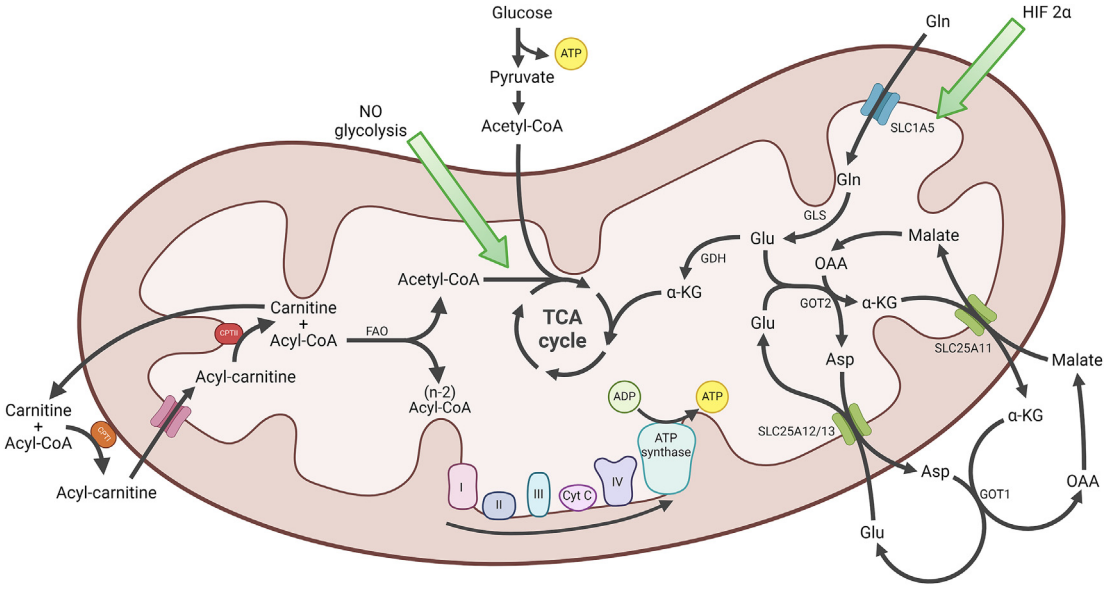

Figure 1: Mitochondrial metabolism.

shorter products to mitochondria for further processing. This coordinated action results in the production of acetyl-CoA and ATP, essential for cellular energy metabolism. The contribution of peroxisomes to β-oxidation highlights their critical role in lipid metabolism and cellular signaling, underscoring the interconnectedness of cellular organelles in regulating metabolic pathways [29].

Fatty acids (FAs) serve as energy-rich molecules and are preferred substrates for energy storage as triacylglycerides (TAGs) [30]. The initial step involves the cleavage of acyl chains from the glycerol backbone, followed by the activation of free FAs through CoA coupling [30]. Subsequently, these activated FAs are transported into the mitochondria for degradation [30]. Recent research has revealed the presence of distinct pancreatic cancer stem cells (CSC) with specific and varied energetic metabolism [17]. Notably, drug-resistant cells with an increased OCR demonstrated a reversal of this phenotype upon treatment with Etomoxir, an inhibitor of FAO, indicating that FAO drives the elevated maximal OCR observed in drug-resistant CSCs [17]. Hypoxia, a critical aspect in PDAC, is regulated by continuous tumor cell proliferation and abnormal blood vessel formation, leading to oxygen deprivation [31]. Hypoxia induces metabolic reprogramming to support tumor cell proliferation, a process primarily mediated by hypoxia-inducible factor 1-α (HIF1α) [31]. Stabilization of HIF1α reduces the expression of FAO enzymes at both the transcriptional and protein levels [31]. The decreased FAO rate triggers autophagy by modulating acetyl-CoA levels within tumor cells. Notably, FAO is crucial to maintaining acetyl-CoA levels, and a lower FAO rate correlates with reduced LC3 acetylation, resulting in autophagy induction that ultimately sustains PDAC growth and chemoresistance under hypoxic conditions [31]. Recent studies have revealed the significance of FAO in IPMN and its role in the early stages of pancreatic tumorigenesis [17]. IPMN relies on FAO-mediated OXPHOS to regulate a stemness signature, maintaining and expanding a population of cells with stem cell-like properties crucial for tumor initiation and progression [17]. This reliance on FAO suggests its essential role in the early stages of pancreatic tumorigenesis, supporting energy demands and sustaining stem-like properties in IPMN cells [17].

2.3. Gln metabolism

Gln, the most abundant amino acid found in plasma, serves as a crucial nitrogen source for synthesizing macromolecules like DNA and RNA, as well as for energy production and metabolite generation [32]. This amino acid undergoes catabolism, known as glutaminolysis, primarily within mitochondria, facilitated by various carriers (Figure 1). The heightened demand for Gln in cancer cells often results in the overexpression of Gln-specific transporters [33].

Recent research has highlighted the importance of a specific variant of the SLC1A5 transporter in pancreatic cancer progression [22]. This variant, transcribed from an alternative transcription initiation site, features an N-terminal mitochondrial targeting sequence that directs it to the inner mitochondrial membrane. Its upregulation has been associated with several cancers, including pancreatic cancer, and is linked to hypoxic conditions through HIF-2α activation [22]-Under normoxic and glucose-rich conditions, cancer cells do not heavily rely on Gln for ATP generation. However, in glucose-deprived or hypoxic environments, Gln becomes indispensable for ATP production, a compensatory mechanism primarily facilitated by the SLC1A5 variant expression [22]. Moreover, the SLC1A5 variant plays a pivotal role in Gln-mediated GSH synthesis, crucial for maintaining cellular redox balance and conferring resistance to chemotherapy drugs like Gemcitabine under hypoxic conditions [22,33]. Further studies have elucidated the role of mitochondrial glutaminolysis in regulating hypoxia, which influences chemoresistance in PDAC cells [34]. Enhanced Gln flux exacerbates intracellular hypoxia via increased oxygen consumption, leading to chemoresistance [22,34]. OCR values could potentially serve as markers for assessing drug responsiveness in PDAC, suggesting the targeting of this axis as a promising strategy to overcome chemoresistance [22,34]. Within mitochondria, Gln is deaminated into glutamate (Glu) by glutaminase (GLS), an enzyme often overexpressed in cancer cells, initiating the rate-limiting step of glutaminolysis, a process commonly dysregulated in various types of cancer, including pancreatic cancer [33]. Glu serves as a vital component for anaplerosis, replenishing metabolic intermediates in the TCA cycle [33]. Additionally, in PDAC, mitochondrial aspartate transaminase (GOT2) plays a pivotal role in the malate-aspartate

shuttle by utilizing Glu, a process essential for maintaining cellular redox balance [34,35].
Mitochondrial Gln metabolism also plays a role in regulating senescence in PDAC cells, with GLS inhibition or downregulation resulting in increased senescence induction [35]. Notably, senescence induction is dependent on GOT2 expression, as its knockdown leads to Reactive Oxygen Species (ROS) accumulation and senescence in PDAC cells [34,35].

2.4. Ion dynamics in PDAC Mitochondria

In PDAC, mitochondria exhibit significant alterations in ion dynamics that play a role in tumor metabolism, resistance to cell death, and chemoresistance. These changes are part of the rewired bioenergetics and metabolic pathways described earlier. One of the most well-characterized alterations concerns mitochondrial calcium (Ca^{2+}), which is mirrored by the upregulation of the mitochondrial calcium uniporter (MCU). The MCU complex is a protein complex involved in cytosolic calcium buffering via mitochondrial intake, which further promotes mitochondrial oxygen consumption [36,37].
The increase in the MCU has been linked to the acquisition of metastatic traits in PDAC [37], suggesting a strong correlation between altered mitochondrial calcium homeostasis and tumor aggressiveness [38]. Intriguingly, elevated MCU activity has also been shown to sensitize PDAC cells to ferroptosis, a form of iron-dependent cell death [37]. This dual role highlights a potential therapeutic strategy by exploiting mitochondrial calcium dysregulation to trigger ferroptosis in PDAC.
In line with sensitivity to ferroptosis, aggressive PDACs demonstrate a marked dependency on iron. These tumors enhance iron import via the transferrin receptor (TFRC) to support OXPHOS [39]. Moreover, iron integration into mitochondria is facilitated by upregulated mitochondrial iron transporters, which have also been found to be elevated in PDAC [40]. This increased mitochondrial iron flux further underscores the critical interplay between mitochondrial function and PDAC progression.
Beyond calcium and iron, alterations in potassium (K^+) dynamics have been observed in PDAC. Tumors exhibit a dependency on potassium channels to regulate mitochondrial K^+ uptake, which is crucial for maintaining mitochondrial function and cancer cell survival [41,42]. These findings position mitochondrial potassium handling as another potential vulnerability in PDAC that could be therapeutically exploited. Hence, the dysregulation of mitochondrial calcium, iron, and potassium ion homeostasis underscores the central role of mitochondrial ion dynamics in PDAC progression. The alterations in these dynamics warrant further investigation for their potential as novel therapeutic targets.
Mitochondria can utilize different substrates to fuel the TCA cycle and the electron transport chain. It can directly use acetyl-CoA or can obtain this substrate from FAO. Fatty acids are carried within mitochondria after the conjugation with carnitine, reaction mediated by transferases such as carnitine palmitoyltransferase I (CPTI). The TCA can be replenished α-ketoglutarate (α-KG) produced from the conversion of Glu derived from glutamine (Gln) catabolism. However, Glu can be also used by GOT2, which is an enzyme involved in malate-aspartate shuttle. GLS glutaminase; GDH Glu dehydrogenase; CPTII carnitine palmitoyltransferase II; GOT1 aspartate aminotransferase; OAA oxaloacetate; Asp aspartate.

3. MITOPHAGY AND MITOCHONDRIAL DYNAMICS ROLE IN PDAC

Mitochondrial dynamics and mitophagy are increasingly recognized as key features of cancer, and PDAC is no exception [43]. Mitophagy is a type of selective autophagy that serves as a quality control mechanism to regulate mitochondrial dynamics. Fine tuning between biogenesis and mitophagy is crucial for maintaining homeostatic fusion and fission cycles and removing damaged organelles. Mitophagy is divided into ubiquitin-dependent and -indipendent pathways, depending on the specific mechanisms of the receptors involved [44]. The PINK1 and PRKN/PARK2 axis, sometimes also referred as the “canonical pathway”, coordinates ubiquitin-dependent mitophagy, with PINK1 kinase triggered when mitochondria are depolarized [45,46]. The buildup of PINK1 on mitochondrial surfaces promotes the recruitment and phosphorylation of Parkin, an E3 ubiquitin-ligase that ubiquitinates and tags damaged mitochondria for degradation [44]. Newly added ubiquitin groups are then phosphorylated by PINK1, generating phospho-ubiquitin chains that act as a docking site to recruit adaptor proteins [44]. These adaptor proteins mediate the interaction with the microtubule-associated protein light chain 3 (LC3). In turns, LC3 initiates the formation of the mitophagosome, the double-membrane structure that engulfs the mitochondria and subsequently fuses with lysosomes, leading to their acidic digestion and degradation [44]. In response to stress conditions, such as hypoxia, an ubiquitin-independent mitophagy pathway can be activated. This “non-canonical” pathway involves transcriptional upregulation of the outer mitochondrial membrane proteins BCL2 interacting protein 3 (BNIP3) and BNIP3-like protein (BNIP3L), which function as ubiquitin-independent autophagy receptors [47]. Hypoxia-induced mitophagy occurs in a PINK1-PRKN independent manner by stabilization and activation of the transcription factor HIF1A (hypoxia inducible factor 1 subunit alpha), leading to expression of BNIP3 and BNIP3L, which interact with Atg-family proteins [47].

3.1. Dysregulation of mitophagy contributes to tumorigenesis

In PDAC, depletion of key autophagic components PINK1 and PARK2 accelerates mutant Kras-driven pancreatic tumorigenesis *in vivo* through failed SLC25A37/SLC25A28 degradation, mitochondrial iron overload, and HIF1A aberrant activation [48]. Mitochondrial iron-mediated DNA damage also activates the inflammasome component AIM2, stimulating CD247 expression and possibly leading to PDAC immune-surveillance escape [48]. Interestingly, PINK1 and PRKN can also have independent functions. Glycolysis suppression in PANC-1 cell line induces mitochondria fusion and increased mitochondrial biogenesis through PGC1-α transcriptional up-regulation [49]. Following reduced glycolytic flux, PINK1 was stabilized on mitochondria, contributing to damaged organelles clearance and maintenance of correct mitochondrial functionality. In contrast, Parkin knockdown did not affect mitophagy nor MMP. Thus, PINK1-dependent mitophagy is required for metabolic reprogramming of pancreatic cancer *in vitro* [49]. PINK1/PRKN mitophagic axis is activated upon treatment of the pro-apoptotic phytochemical Rocaglamide-A, which leads to toxic ROS accumulation. However, silencing Parkin can increase cancer cells sensitivity to Roc-A, possibly indicating mitophagy as a protection mechanism activated in response to treatment [50]. In line with that, acid b-glucosidase (GBA) knock-down reduced MMP and perturbed the mitophagy flux, leading to ROS accumulation. GBA reduction increased Gemcitabine chemotherapeutic effects, supporting the role of mitophagy as a protection mechanism [51]. STOML2, a protein implicated in mitochondria stability, can repress full-length PINK1 and overall autophagy levels in pancreatic cancer cells by directly binding PARL. STOML2 inhibition reduced total mitochondrial mass and size, thus promoting mitochondria fragmentation and mitophagy, concomitantly driving Gemcitabine resistance. Consistently, inhibiting PINK1 reversed the chemoresistance phenotype under STOML2

downregulation [52]. Mitophagy can be induced also by targeting mtDNA, as miriplatin-loaded liposomes induce LONP1 protease to degrade POLG and TFAM, consequently activating the PINK1/Parkin axis and suppressing pancreatic cancer cells proliferation through mitophagy induction [53]. Late ATG4D-driven mitophagy is regulated by PPARy protein through direct binding on SOD2 gene promoter. Blockade of the PPARγ/SOD2 pathway pushes ATG4D mitochondria localization and mitophagy activation, contributing to increased mitochondrial ROS production, mitochondrial depolarization and promotion of cancer cell apoptosis. Therefore, PPARγ/SOD2 axis could protect against mitochondrial ROS-dependent apoptosis via inhibiting ATG4D-mediated mitophagy [54]. Confirming the essential role of mitochondrial dynamics in PDAC, researchers have begun constructing mitophagy-related gene signatures to predict patient prognosis and treatment response. PRKN, SRC, and VDAC1 mitochondrial genes may constitute a three-gene prognostic marker able to stratify PC patients and predict sensitivity to paclitaxel and erlotinib [55]. Similarly, CAST, CCDC6 and ERLIN1 were overexpressed in a "high mitophagy" pancreatic cancer subtype, and correlated with resistance to treatments and worse prognosis [56]. Overall, mitophagy seems to exert a dual, context-specific role in PDAC, being simultaneously able to promote a protective mechanism by removing damaged organelles and reducing ROS accumulation, but also to prompt cancer cells to apoptosis in response to treatments in case of critical mitochondrial stress and damage (Figure 2). Understanding the factors that specifically determine mitophagy-driven promotion or suppression of pancreatic tumorigenesis remains a challenging task for the future.

3.2. Mitochondrial dynamics regulation in pancreatic cancer

Previous reports highlighted that PDAC preferentially impinges on mitochondria fragmentation to support its energetic needs, with some controversial findings to highlight the delicate role of fission/fusion equilibrium [23]. Mitochondrial fragmentation, primarily controlled by the fission-mediating GTPase Drp1, is linked to the RAS/MAPK pathway activation. Inhibition of ERK2-mediated Drp1 phosphorylation is sufficient to block PDAC xenograft growth [57]. Accordingly, loss of Drp1 decreases PDAC progression *in vivo*, inhibiting the transition to PanIN3 and increasing mice overall survival [58]. This was due to a massive metabolic reprogramming that included increased glycolytic flux through HK2 increased expression, impaired fatty acid oxidation and dysfunctional mitochondrial respiration. In murine pancreatic ductal organoids, expression of KRASG12D disrupted the mitochondrial network and decreased mtDNA-to-nuclearDNA ratio, suggesting organelle fragmentation and increased mitophagy [59]. This was associated with increased expression of BNIP3L/NIX and lipidated LC3, but not PINK1/PARK2, suggesting a possible involvement of the ubiquitin-independent autophagic pathway. Loss of Nix restores functional mitochondria and reduces cancer progression *in vivo*. In line with these findings, Drp1 was found to be upregulated in several pancreatic cancer cell lines and tissues and correlated with increased metastatic potential [59]. Drp1 expression is significantly upregulated in pancreatic cancer cell lines and tissue samples, primarily due to the downregulation of miR-29a, a tumor-suppressor miRNA [60]. This downregulation contributes to poor survival outcomes in pancreatic cancer patients, further confirming the pro-tumorigenic role of Drp1 [60]. Overexpression of the SMDT1 subunit of calcium transporter complex (MCU) increases mitochondrial fragmentation and Drp1 phosphorylation but correlates with better patient overall survival [61]. Similarly, UCA1 lnRNA is upregulated in PDAC patients, but its knockdown correlates with increased Drp1 phosphorylation and increased mitochondria-driven apoptosis [62]. These findings may suggest possible differences between acute and chronic Drp1 perturbation. Mitochondrial network fragmentation was also found to be driven by loss of SMAD4, followed by overall decreased respiratory chain functions. SMAD4 loss correlated with hyperactivation of the MAPK/ERK pathway and resistance to mitochondrial targeting via Mitochondria-targeted Metformin (MitoMet). Silencing of ERK2 or Parkin similarly decreased mitophagy and promoted vulnerability to MitoMet, confirming the link between mitophagy, MAPK/ERK signaling and SMAD4 loss in PDAC [63]. Interestingly, a recent work shed light on the connection between the chaperome and mitochondrial dynamics in pancreatic cancer [64]. Suppression of the HSP70 chaperone protein led to decreased Drp1 phosphorylation through suppression of PINK1 activity, with concomitant ROS production and activation of AMPK-mediated autophagic flux. Parallel inhibition of the HSP70 and autophagic components synergistically induced apoptosis

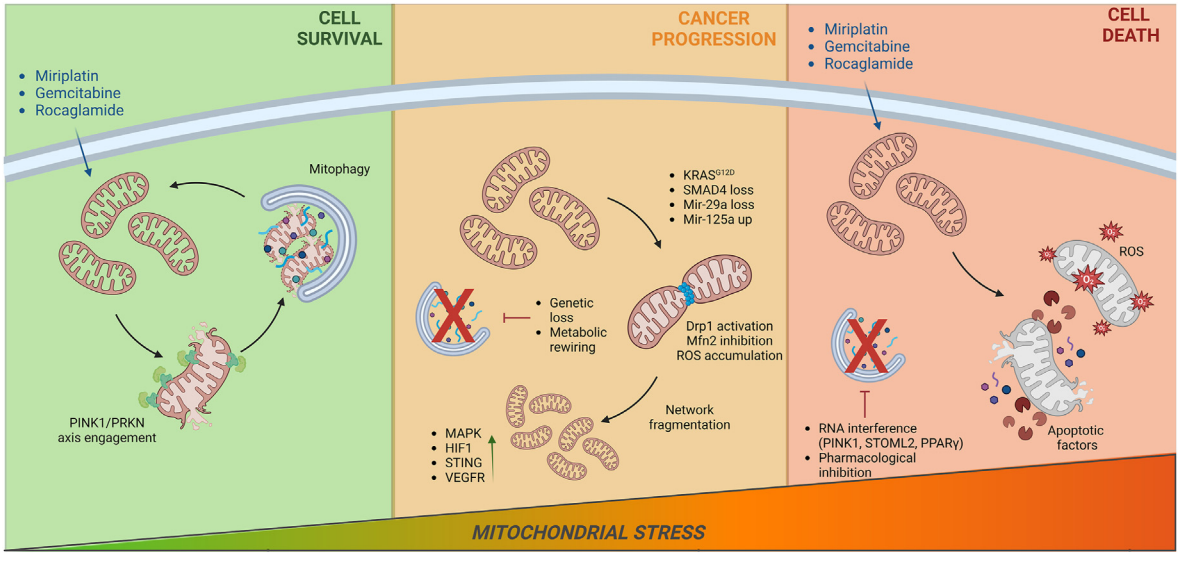

Figure 2: Roles of mitophagy and mitochondrial dynamics equilibrium in PDAC.

in vitro and impaired tumor progression *in vivo*, confirming mitochondrial dynamics manipulation as a new therapeutic avenue [64]. In contrast to fragmentation, mitochondrial fusion mediated by Mitofusins (Mfn) family proteins, particularly Mfn2, exhibits anti-tumorigenic properties. Mfn2 is a transmembrane GTPase mainly expressed in the mitochondrial outer membrane. Adenovirus-mediated overexpression of Mfn2 in PDAC cell lines downregulated p62 and Bcl-2 anti-apoptotic markers by inducing autophagy through the PI3K/AKT/mTOR pathway, reducing cancer cells proliferation [65]. Knockdown of miR-125a increased Mfn2 expression, reducing mitochondrial fragmentation, preserving mitochondria membrane potential and reducing pro-apoptotic markers in PANC-1 cell line [66]. Mfn2 was downregulated in PC patients and it was proposed to act as potential anti-angiogenic factor by blocking VEGFA/VEGFR2 in HUVEC, but similar findings *in vivo* still lack, and the underlying molecular mechanism of MFN2-induced angiogenic alterations remains unexplored [67]. Mfn1/2 were also found to control ferroptosis, through direct interaction with STING1 ER protein. Genetic depletion of Mfn1 or STING1 in PDAC xenografts reduced cancer sensitivity to erastin-induced ferroptosis independently from PINK1-dependent mitophagy [68]. Additionally, acute ferroptosis induction by mitochondria-targeting agent Myoferlin induces aberrant mitophagy and ferroptotic cancer cell death, and synergistically potentiates erastin effects [69], potentially opening new combinatorial treatment avenues. Crucially, Drp1 and Mfn alterations are not only consequences of rewired mitochondrial network but can be directly exploited as cancer vulnerabilities [70]. Restoring normal mitochondrial networks via Drp1 inhibition or Mfn2 overexpression was sufficient to suppress tumor growth and improve survival in preclinical models. On this basis, the FDA-approved anti-arthritis drug leflunomide was able to increase Mfn2 expression levels and it was proposed to be repurposed as chemotherapeutics [70]. Fully understanding the intricate balance of mitophagy and mitochondrial dynamics in PDAC will provide insights into potential therapeutic targets and prognostic markers for this aggressive cancer.

Mitophagic clearance of damaged organelles can lead to drug resistance and cell survival (left). Silencing of key components (PINK1) or indirect regulators (STOML2, PPARγ) can restore sensitivity to treatments and lead to apoptosis (right) [50,52,54]. In parallel, aberrant mitophagy activation, such as upon Miriplatin treatment, can induce ROS accumulation and direct cell death (right). Common PDAC mutations such as KRASG12D or SMAD4 loss can lead to mitochondria network fragmentation and increased cancer aggressiveness through Drp1 upregulation, MAPK pathway activation, and increased angiogenesis (middle) [57–60,63]. Chronic genetic loss of key autophagic components contributes to PDAC tumorigenesis by overriding mitochondrial fission, inducing HIF1 accumulation and potentiating immune escape (middle) [48].

4. MITOCHONDRIA AT THE CENTER OF TUMOR MICROENVIRONMENT CROSSTALK

It is now firmly recognized that cancer cells and the tumor microenvironment (TME), including cancer-associated fibroblasts (CAFs) and the immune compartment, establish a strict crosstalk to promote cancer survival and fostering glycolytic shift, nutrient uptake, and de novo biosynthesis. As principal orchestrators of cell metabolism and energetic processes, mitochondria are at the center of such crosstalk. In pancreatic cancer, CAF-derived exosomes (CDEs) deliver intact metabolites such as amino acids, lipids, and metabolic intermediates. Moreover, CDEs exacerbate mitochondrial network imbalance, thereby promoting a glycolytic shift and enhancing cancer aggressiveness [71]. Mutated KRAS, the principal oncogenic driver in PDAC, can engage CAFs in a reciprocal crosstalk that multiplies the number of signaling nodes and extends tumor cell signaling beyond cell-autonomous KRASG12D activation. Reciprocal signaling increased mitochondrial polarization, superoxide production, and spare respiratory capacity via IGF1R/AKT axis, demonstrating that mitochondrial performance can be regulated by heterocellular communication [72]. Stroma-associated pancreatic stellate cells (PSCs) support cancer metabolism through secretion of non-essential amino acids, facilitating biosynthesis in the nutrient-poor condition of pancreatic cancer [73]. PSCs-derived alanine alone is sufficient to enhance PDAC mitochondrial OCR, serving as an alternative carbon source to fuel the TCA cycle in low-glucose conditions. In turn, PDAC cells stimulate the PSCs autophagic process to promote protein catabolism and alanine production and secretion, thus establishing a two-way crosstalk that promotes tumor cells survival. Interestingly, the primary driver of concentrative alanine influx in PDAC cells was demonstrated to be mitochondrial SLC38A2, and disrupting SLC38A2-dependent alanine uptake affected tumor initiation and maintenance in subcutaneous and orthotopic models of PDAC, thus confirming cancer-TME metabolic crosstalk as an actionable therapeutic target [74]. Not only fibroblasts but also immune cells are a fundamental regulator of the complex interplay between TME and cancer.

The ubiquinol-cytochrome c reductase core protein I (UQCRC1), a key component of mitochondrial complex III, exhibited a gradual increase during the progression from PanIN stages to PDAC in KPC mice [75]. This protein was shown to enhance mitochondrial OXPHOS, leading to increased ATP production, which was subsequently released into the extracellular space (eATP) via the pannexin 1 channel [76]. eATP inhibited the cytotoxic effects of natural killer cells by reducing the expression of CCL5 chemokine in cancer cells and altering the balance between activating and inhibitory receptors in NK cells [76]. This work shed light on the possibility to act on mitochondrial activity to improve cancer immunotherapy. Importantly, pancreatic cancer-TME crosstalk can rewire the tumor signaling landscape to achieve adaptation and resistance to therapies. Cancer-associated fibroblasts can provide bioavailable iron to PDAC cells, bypassing the loss of succinate dehydrogenase complex iron sulfur subunit B and promoting resistance to autophagy inhibition [77]. Pancreatic cancer can reshape the fibroblastic phenotype in the surrounding microenvironment through epigenetic reprogramming. The histone trimethyl-transferase SETD2 functions as a tumor suppressor in PDAC. SETD2 loss aberrantly increases H3K27 acetylation and promotes BMP2 signaling, leading to CAFs differentiation to a lipid-rich phenotype. In turn, recruited lipid-rich CAFs provide lipids to fuel mitochondrial OXPHOS, promoting tumor growth [78]. Altogether, it is increasingly clear that pancreatic cancer recruits, reprograms, and exploits the surrounding cell populations to promote its own survival in a harsh, nutrient- and oxygen-poor environment. Moreover, the expanded metabolic network that results from cancer-TME crosstalk often results in acquired therapeutic resistance. Thus, a deeper understanding of the cancer mitochondria-metabolism-TME axis will yield valuable therapeutic opportunities and enhance strategues forcombating pancreatic malignancies.

5. THERAPEUTIC AVENUES: MITOCHONDRIA TARGETING IN PDAC

Within the field of cancer treatment, there has been a notable shift towards exploring mitochondrial metabolism, particularly in the context of PDAC. Emerging treatments include interventions aimed at Gln and fatty acid metabolism, inhibiting TCA cycle precursors, and directly targeting mitochondrial OXPHOS. In particular, some potential cancer

treatment agents are designed to act on the specific mitochondrial complexes, aiming to disrupt cancer cell bioenergetics and growth pathways. The human mitochondrial respiratory chain consists of 5 complexes: NADH-ubiquinone oxidoreductase (CI), succinic acid-ubiquinone oxidoreductase (CII), cytochrome Bc1 complex (CIII), cytochrome C oxidase (CIV), and adenosine triphosphate synthase (CV) [79]. The reliance of cancer cells on the OXPHOS for survival created a therapeutic opportunity, allowing inhibitors of mitochondrial respiration to contribute tumor growth potentially [80,81] (Table 1). The biguanides phenformin and metformin primarily target Complex I, serving as key players in preventing tumor development [82]. Metformin, specifically recognized as a Complex I inhibitor, disrupts both cellular and mitochondrial respiration by impeding Complex I, which is intricately linked to NADH-related respiration [83]. Notably, the combination of metformin with chemotherapy did not result in improved patient survival in clinical investigations involving individuals diagnosed with PDAC [84,85]. However, it was observed that OXPHOS rates display significant variability among tumor samples from different patients, with those exhibiting high OXPHOS levels often showing enrichment in the mitochondrial respiratory complex I. Treating PDAC cells with phenformin and standard chemotherapy (gemcitabine) demonstrated synergistic effects in high OXPHOS cells, suggesting a potential strategy to identify responsive PDAC patients for clinical testing of phenformin in the relevant subpopulations [27]. Metformin is currently under investigation in several ongoing clinical trials aimed at assessing its efficacy and safety across various medical contexts and patient populations, including a single-center study (NCT03889795) investigating its use in combination with digoxin and simvastatin in patients with pancreatic cancer and other advanced solid tumors. This trial constituted an open-label, single-arm dose escalation Phase IB trial, with subjects recruited in cohorts of three individuals for dose escalation. Eligible participants are those with previously treated advanced solid tumors who have experienced disease progression despite receiving established standard therapy. Additionally, there is an ongoing Phase 1b clinical trial assessing the safety and tolerability of Lixumistat (IM156), a novel biguanide and a derivative of metformin, in combination with gemcitabine and nab-paclitaxel for the patients with metastatic PDAC. (NCT05497778). IM156 demonstrated limited efficacy as a monotherapy, indicating that a strategic shift towards exploring rational combinations with other anticancer agents is required [86].

Table 1 — Sites of action of drugs targeting mitochondria and references.

Drug	Target	Reference
Metformin	C1	[84,85]
Lixumistat (IM156)	C1	[86]
Mito-Tam	C1	[63]
Carboxyamidotriazole (CAI)	C1	[90]
Mito-CP	COX IV	[92]
Mito-CP-Ac	CIII	[93]
Doxycycline	Ribosome 28S	[94]
Mitoquinone (Mito-Q)	Induce mitochondrial uncoupling	[97]
Genipin	UCP2	[100]
DZ-SIM	Accumulation in mitochondria	[101]
DX2-201	C1	[103]
Mito-Chlor	mtDNA	[104] [105]
Ruthenium complex	mtDNA	[108]
Devimistat (CPI-613)	α-ketoglutarate dehydrogenase (α-KGDH) and pyruvate dehydrogenase (PDH)	[109]
Ivosidenib	Isocitrate dehydrogenase-1	10.1101/2023.03.29.534596 [110] — not reviewed

The modified formulation, Mito-Tam, which targets tamoxifen to the mitochondria, has been validated as an innovative strategy for treating Her-2 positive breast cancer, by inhibiting complex I and disruption of the respiratory super-complex [87]. In this genetic phenotype, the ETC undergoes reorganization, making Mito-Tam more effective. Mito-Tam demonstrated efficacy in overcoming drug resistance in patients with SMAD family member 4 gene (SMAD4)-deficient or Transforming Growth Factor-β (TGF-β) signaling-mediated pancreatic cancer [63]. This highlights its potential as a rational predictive marker for mitochondrial-targeted therapy in pancreatic cancer patients expressing SMAD4. A phase I clinical study is running to assess Mito-Tam safety, determining the maximum tolerated dose, establishing the appropriate dose, and identifying potential target groups for subsequent treatment of malignant tumors [88] (EudraCT 2017-004441-25). Carboxyamidotriazole (CAI) functions as a cytostatic inhibitor of non-voltage-operated calcium channels and pathways reliant on calcium channel-mediated signaling. CAI has been proven to decrease mitochondrial oxygen consumption in cancer cells by inhibiting complex I [89]. Its efficacy extends to chemotherapy-resistant pancreatic cancer when combined with the glycolysis inhibitor 2-DG [90].

Mito-CP, a superoxide dismutase mimetic, composed of 3-carboxyl proxyl (CP) nitroxide conjugated to TPP+, has shown the targeted anti-proliferative and cytotoxic effects against both pancreatic and breast cancer cells, with minimal impact on non-transformed cells [91]. The pivotal factor for its effectiveness in tumor inhibition lies in the essential mitochondria-specific delivery of the CP fragment of Mito-CP [92]. To curb the proliferation of pancreatic cancer cells, Mito-CP, and its synthetic derivative, Mito-CP-Ac (targeting complex III), act by suppressing cellular energy metabolism [91]. They trigger the activation of the AMPK energy-sensing pathway and bring about changes in the roles of glycolysis and citrate within mitochondrial bioenergy metabolism. This comprehensive approach presents a promising strategy to effectively disrupt the energy dynamics underlying the uncontrolled growth of pancreatic cancer cells [93].

Specific anti-parasitic medications, such as doxycycline, have been observed to affect mitochondrial function, exhibiting potential efficacy in preclinical cancer models. Doxycycline, also known for malaria prevention, inhibited mitochondrial protein translation by targeting the small mitochondrial ribosome (28S), re-sensitizing cancer cells (e.g., colon and pancreatic) to gemcitabine by reducing mitochondrial ATP generation, slowing proliferation, and enhancing gemcitabine efficacy [94].

Mitoquinone (Mito-Q), a targeted antioxidant focusing on mitochondria, effectively eliminates excessive ROS, that consists of TPP+ and the ubiquinone portion of CoQ [95,96]. By inducing mitochondrial uncoupling, Mito-Q reduces ATP, MMP, and increases mitochondrial energy production. At therapeutic doses, Mito-Q inhibits pancreatic cancer cell migration, invasion, and clonogenicity. It also significantly reduces the metastatic homing of human pancreatic cancer cells in mice by about 50%, suggesting its potential to prevent the metastasis development in humans [97].

Uncoupling protein 2 (UCP2), part of the mitochondrial anion transporter superfamily, resides in the inner mitochondrial membrane, functioning as a proton transporter. Deletion of the UCP2 in oocytes enhances thermogenesis, reduces ATP, and decreases MMP, implicating UCP2 downregulation in Mito-Q-induced mitochondrial uncoupling [98]. UCP2 plays a dual role in PDAC, being downregulated during tumorigenesis initiation but overexpressed later, contributing to tumour maintenance and treatment resistance [99]. Combining genipin, a

UCP2 inhibitor, with gemcitabine effectively increases ROS production and inhibits cell proliferation [100], suggesting a potent strategy for inducing the cancer cell death in PDAC by combining genipin with ROS-inducing chemotherapies.

New molecules have been developed to target mitochondria in pancreatic cancer cells. DZ-SIM, a molecule comprising a tumor-targeting ligand, near-infrared organic heptamethine carbocyanine dye (HMCD), and HMG-CoA inhibitor simvastatin, notably inhibits tumor growth and re-sensitizes the therapeutically resistant PDAC cells to conventional therapies in mouse models [101]. DZ-SIM induces cancer cell death by accumulating in mitochondria, reducing mitochondrial bioenergetics, including oxygen consumption and ATP production, and also by increasing ROS levels [101]).

DX2-201, a specific inhibitor of OXPHOS, was introduced to target NDUFS7, an essential component of complex I [102]. DX2-201 inhibits complex I activity, suppressing mitochondrial function and hindering proliferation in various pancreatic cancer cell lines. Notably, its metabolically stable analogue DX3-213B significantly retards tumor growth *in vivo*. DX2-201 exhibits synergy with radiation, PARP inhibitors, and metabolic modulators [103]. Combining DX2-201 with 2-deoxyglucose (2-DG) enhances sensitivity in pancreatic cancer cells both *in vitro* and *in vivo*. A Comprehensive analysis of cells resistant to complex I treatment identifies GNAS as a potential biomarker for responsive patient populations. This validates NDUFS7 as a novel therapeutic target and positions DX2-201 as a first-in-class NDUFS7 inhibitor, demonstrating substantial single-agent efficacy and remarkable synergy with select drugs, providing a promising strategy to overcome drug resistance [103].

In addition to these strategies, researchers are exploring alternative approaches, such as targeting mitochondrial DNA (mtDNA). Mito-Chlor, a derivative of the nitrogen mustard chlorambucil, exemplifies an approach that improves chlorambucil's localization within mitochondria [104]. By targeting mitochondrial DNA, it induced cell cycle arrest and significantly enhances the killing of breast cancer and pancreatic cancer cell lines, demonstrating its efficacy in a distinct approach [104]. In a separate investigation involving pancreatic cancer cells, Mito-Chlor was found to inhibit nascent transcription of mitochondrial DNA, leading to reduced steady-state levels of subunits of mitochondrially-encoded NADH [105]. The study also highlighted the discovery of a novel mitochondrial transcriptional inhibitor, SQD1, which, when combined with Mito-Chlor, induces an increase in ROS levels within both the mitochondria and the cytoplasm. Additionally, a ruthenium complex, initially developed as a DNA-targeting anticancer agent, has shown multifaceted mechanisms of action [106]. Some of these complexes target telomere DNA, interfering with DNA replication and transcription, while others inhibit related enzymes. Additionally, ruthenium complexes can disrupt the cell cycle and induce the formation of DNA photo crosslinking products. This prevents RNA polymerization enzymes or exonucleases from binding to DNA, ultimately leading to tumor cell apoptosis. Specific studies highlighted the stable binding of certain dinuclear and polynuclear polypyridyl complexes to the G-quadruplex (G4-DNA) structure of telomere DNA. This inhibits telomerase activity and hinders DNA replication, preventing the transformation of normal cells into immortalized tumor cells [107]. It was shown that a specific ruthenium complex (Ru1), which contains a bipyridine and a terpyridine ligand, inhibits pancreatic CSCs OXPHOS, showing remarkable anti-cancer activity across various human pancreatic, colorectal, and osteosarcoma patient-derived xenograft models [108]. Ru1 binds to mitochondrial DNA and creates covalent DNA adducts, particularly through reactions with the N7 of guanines. It inhibits OXPHOS complex-associated transcription and reduces critical components for cell survival, unveiling a promising strategy for the targeting CSCs' OXPHOS in different cancer types.

The TCA cycle represents a key target in cancer cell metabolism. Devimistat (CPI-613), a novel lipoate analogue, inhibits α-ketoglutarate dehydrogenase (α-KGDH) and pyruvate dehydrogenase (PDH), two critical gatekeeper enzymes regulating the entry of Gln- and pyruvate-derived carbons into the TCA cycle [109]. Despite showing safety and tolerability in phase I and II trials for metastatic pancreatic cancer, CPI-613's clinical efficacy in phase III trials (NCT03504423) for PDAC has not demonstrated significant improvements in overall survival [109]. Currently, there is another Phase 1 clinical trial (NCT05325281) underway, which is investigating the use of Devimistat in combination with chemoradiation for patients diagnosed with pancreatic cancer.

Ivosidenib, a small molecule inhibitor targeting isocitrate dehydrogenase-1 (IDH1), plays a crucial role in the TCA cycle by catalyzing the interconversion of isocitrate and alpha-ketoglutarate. Suppression of wild-type IDH1 (wt IDH1) leads to impaired redox balance, increased ROS levels, and heightened apoptosis induced by chemotherapy in pancreatic cancer cells *in vitro*. *In vivo* experiments have further demonstrated that inhibiting wtIDH1 enhances the anti-tumor effects of chemotherapy in both patient-derived xenografts and murine models of pancreatic cancer. This highlights the potential of Ivosidenib as a therapeutic strategy for improving the efficacy of chemotherapy in pancreatic cancer treatment [110]. At present, an ongoing Phase 1 clinical trial is assessing the use of Ivosidenib in combination with mFOLFIRINOX in patients diagnosed with resectable PDAC (NCT05209074).

In summary, the focus on mitochondrial metabolism as a therapeutic approach for PDAC unveils the diverse strategies, from targeting specific complexes to disrupting cancer cell bioenergetics. These varied approaches hold promise for advancing PDAC treatment efficacy, providing encouraging prospects for future developments in cancer therapeutics.

6. CONCLUSION

The intricate interplay between mitochondrial dynamics and mitophagy emerges as a pivotal aspect in the pathogenesis and progression of PDAC. Mitophagy, as a selective autophagic process, finely regulates mitochondrial homeostasis by orchestrating the balance between mitochondrial biogenesis and the clearance of damaged organelles. Dysregulation of the mitophagy pathways contributes significantly to tumorigenesis in PDAC, highlighting its multifaceted role in cancer biology. Furthermore, emerging evidence suggests a dual role for mitophagy in PDAC, capable of both promoting apoptosis in response to treatment and serving as a protective mechanism against the-accumulation of ROS. Understanding the intricate molecular mechanisms underlying mitophagy dysregulation in PDAC presents a challenging yet promising avenue for the development of novel therapeutic strategies and prognostic markers. Moreover, the regulation of mitochondrial dynamics, characterized by alterations in fission and fusion processes, profoundly impacts PDAC progression, offering additional targets for therapeutic intervention. Exploiting vulnerabilities associated with mitochondrial dynamics alterations presents a promising therapeutic approach, as evidenced by preclinical studies demonstrating the efficacy of targeting key regulators such as Drp1 and Mfn2. Fully comprehending the delicate equilibrium between mitophagy, the process of removing damaged mitochondria, and mitochondrial dynamics, the continuous fusion and fission events regulating mitochondrial shape and function holds significant potential

for improving patient outcomes and developing more effective therapeutic interventions for this aggressive malignancy.

In conclusion, the exploration of mitochondrial metabolism as a therapeutic avenue for PDAC presents a diverse array of strategies, ranging from targeting specific complexes to disrupting cancer cell bioenergetics. These multifaceted approaches offer promising prospects for enhancing PDAC treatment efficacy and represent avenues for future advancements in cancer therapeutics. The ongoing clinical trials investigating various compounds and combinations underscore the continued efforts to refine and optimize treatments for PDAC, highlighting the dynamic landscape of research in this field. Through continued exploration and innovation, there is hope for improving outcomes and quality of life for patients battling this challenging disease.

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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 4.0 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.

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DATA AVAILABILITY

Data will be made available on request.

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