Metabolic Reprogramming in Pancreatic Ductal Adenocarcinoma

Subjects: Oncology

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Metabolism plays a fundamental role in both human physiology and pathology, including pancreatic ductal adenocarcinoma (PDAC) and other tumors. Anabolic and catabolic processes do not only have energetic implications but are tightly associated with other cellular activities, such as DNA duplication, redox reactions, and cell homeostasis. PDAC displays a marked metabolic phenotype and the observed reduction in tumor growth induced by calorie restriction with in vivo models supports the crucial role of metabolism in this cancer type. The aggressiveness of PDAC might, therefore, be reduced by interventions on bioenergetic circuits.

PDAC metabolism glucose amino acids lipids

1. Activation and Maintenance of Glycoltyc Flux

In PDAC, the expression of glycolytic genes is regulated at both transcriptional and post-transcriptional level via oncogenic KRAS [1]. KRAS signaling plays a crucial role in regulating transcription of both glucose transporters (GLUTs) and key glycolysis genes [2]. Glucose need of the PDAC system seems to be due to the expression of facilitated GLUTS and sodium-glucose transporter (SGLTs); PDAC tumors showed both increased pyruvate carboxylation and glucose oxidation via pyruvate dehydrogenase in vivo [3]. PDAC progression is induced by the activation of mutant KRAS, resulting in an increase in GLUTs, such as GLUT-1, from low- to high-grade dysplasia. Oxygen is related to GLUT-1 expression through hypoxia inducible factor 1 alpha (HIF-1α). In patients with low expression levels of GLUT-1, neoadjuvant chemotherapy such as TS-1 showed better therapeutic response and better prognosis than in those with higher GLUT-1 expression levels [4]. PDAC tumor biology relies on hypoxia and HIF1α signaling to control tumor-promoting stromal programs, which facilitate progression and tumor cell invasivenes [5]. Hypoxia-activated stromal cells contribute to the invasive growth of PDAC cells by releasing soluble proteins, such as MMP10, and enhance the levels of inflammatory and angiogenetic factors including IL1α, TIE family members, and VEGF-A. MMP10, the main stromal protein driving EMT in tumor cells [6], is reported as a stellate cell product [7], [8]. IL1α was shown to be released by both stromal cells and PDAC cells, thus promoting tumor growth [9] in an autocrine manner [10], and stimulated the fibrotic component [11]. TIE1 upregulation and increased TIE2 transcription in hypoxic stellate cells are crucial for the remodeling and maturation of tumor vasculature [12], forming a complex with angiopoietins and sustaining TIE2 signaling in contacting cells [13]. Altered levels of VEGF-A found in PDAC indicate an imbalance in normal angiogenetic processes [14]. In particular, the high extracellular matrix component associated with vasculature collapse resulted in an increased hypoxic

environment, partly explaining the low efficacy of antiangiogenic drugs in this cancer [15] and the inefficient delivery of chemotherapeutic agents [16]. Thus emphasizing a recently described stroma-targeting therapy that aims to reduce the stromal component to improve target achievement [17]. According to the transcriptomic profiles of PDAC patients, ubiquitin specific peptidase 25 (USP25) depletion was linked to decreased levels of HIF-1α, GLUT-1, and glycolysis signaling. This suggests that USP25 complex deubiquitinates and stabilizes the HIF-1 α transcription factor from a mechanistic point of view [18]. SGLTs also play a functional role in glucose uptake, since the selective inhibition of SGLT2 in mouse models of pancreatic cancers led to a decrease in glucose uptake [19]. Furthermore, the hypoxic environment is essential for maximizing energy yield and biomass production, which are ensured by the lack of oxygen, which promotes conversion of pyruvate into lactate by Lactate Dehydrogenase A [20]. In such way, ATP is generated and an increased amount of lactic acid is released outside of the cell, acidifying the microenvironment and in turn facilitating PDAC progression [21]. Monocarboxylate transporters (MCTs), which transport lactate, are abundantly expressed in PDAC [22]. MCT1 and MCT4 regulate lactate efflux through KRAS-dependent signaling, releasing intracellular accumulated lactate and maintaining intracellular pH [23]. This process facilitates the oxidation of nicotinamide adenine dinucleotide (NADH) to NAD^+, a cofactor for oxidizing glyceraldehyde 3-phosphate and driving glycolysis [24]. The glycolytic shift meets the energy demands required for tumor growth, as well as supplying the building blocks for biochemical reactions and intermediates [25]. MUC1 and MUC13 transporters also stabilize transcription of HIF-1α during hypoxia conditions and induce the expression of glycolytic genes [26] associated with poor survival rates in PDAC patients [18]. In contrast, CD147 works as a chaperone for the membrane localization of MCT1 and MCT4, both expressed in PDAC cells [27]. Whether the interaction between CD147 and MCT is related to PDAC progression has not yet been determined [28]; however, depletion of MCT4 reduces cell viability, whereas depletion of CD147 affects tumor growth in xenograft models [23], [29]. As regards the glycolytic flux of anabolic pathways in PDAC, the pentose phosphate pathway (PPP) is a branch of glycolysis that directs glucose flux to oxidation and regulates NADP and nucleic acid synthesis, which ensure fatty acid (FA) production and cell survival under stress conditions [30]. According to a metabolomic analysis of PDAC, the adaptation to acidosis status increases glucose and decreases glycolysis, driving a shift to PPP [31], [21]. PPP occurs in two different ways: oxidatively and non-oxidatively. The oxidative arm transforms glucose 6-phosphate into ribulose-5-phosphate and CO_2, which are essential for maintaining redox equilibrium under stress conditions [32]. The non-oxidative branch produces glycolytic intermediates, resulting in the production of sugar phosphate, an important precursor for amino acid synthesis, ribose-5-phosphate which is needed for nucleic acid synthesis [33]. Furthermore, oncogenic KRAS selectively activates non-oxidative PPP, possibly via the induction of genes involved in the non-oxidative arm, such as ribulose-5-phosphate isomerase (RPIA) [34]. Low expression levels of RPIA deficits result in reduced KRAS-driven signaling in PDAC cells, indicating the importance of non-oxidative PPP in metabolic function [1]. Growing evidence suggests that non-oxidative PPP contributes to gemcitabine resistance in PDAC and that reduced expression of transketolase is associated with higher gemcitabine sensitivity in PDAC patients, strengthening the therapeutic potential of targeting non-oxidative PPP [26]. Post-transcriptional processes, such as those modulated by microRNAs, are also thought to play an important role in PDAC progression [35]. microRNAs are linked to the regulation of glycolysis in PDAC; the tumor suppressor miR-124 regulates MCT1 [36], resulting in increased intracellular pH that reduced acidic environment and decreased PANC-1 cell proliferation. miR-135 was found significantly overexpressed in PDAC patient samples

compared to normal tissue, and notably associated to a metabolic alteration. It has been observed miR-135 accumulation during glutamine deprivation, promoted by mutant TP53. Specifically, miR-135 targets phosphofructokinase-1 inhibiting aerobic glycolysis and promoting TCA cycle [35]. Some studies have already been conducted on the potential role of mirna as biomarkers of PDAC. miRNA-483-3p and miRNA-21 were found to be significantly higher from blood plasma in PDAC compared to healthy controls, and related to to advanced stage disease [37], [38]. Further functional studies on miR-124 may lead to new therapeutic strategies for PDAC [36].

2. Amino Acids as an External Energy Resource

The PDAC phenotype is also triggered by the rewiring of amino acids, contributing to the metabolic profile of PDAC by regulating cell proliferation, invasion, and redox homeostasis [39]. In cellular hemostasis, glutamine is a multifunctional amino acid that serves as a key energy source [40]. The biological activities of glutamine rangefrom providing energy to stabilizing reducing agents, contributing to the biosynthesis of purines and pyrimidines, and its involvement in PDAC has been recognized [41], [42]. PDAC cells can compensate for the increased metabolic demand either by increasing glutamine production or by increasing glutamine uptake from the environment, thus reducing glutamine levels in blood serum despite the abundance of fibrotic cells in the pancreas [43]. Glutamate-Ammonia Ligase (GLUL), the enzyme responsible for *de novo* production of glutamine, was found elevated in PDAC [44]. Although the cause of this increase is not completely clear, CRISPR/Cas9 ablation of GLUL in PDAC mouse models reduced tumor growth [44]. Metabolic niches also contribute significantly to cancer development and progression. Autophagy plays a pivotal role in supporting the growth of PDAC through fibroblasts [45]. Autophagy allows fibroblasts to break down misfolded proteins and ECM, releasing large quantities of amino acids into the microenvironment [46]. In addition, circulating macromolecules enter PDAC cells using using the Na+-dependent glutamine transporter SLC1A5, in the case of glutammine, or via macropinocytosis/micropinocytosis, for proteins, a mechanism linked to the growth of cancer cells expressing oncogenic *KRAS* [47], [48], [49], [50]. Micropinocytosis inhibitors were found to interfere with this ability in MIAPaCa2 cells, a PDAC model [51]. Glutamine intake is converted into glutamate to feed a complex network of enzymes and intermediates. PDAC utilizes glutamate to activate the tricarboxylic acid (TCA) cycle and electron transport chain after its conversion into alpha-ketoglutarate (αKG) in mitochondria; notably, αKG acts as an epigenetic factor [52]. αKG may also function in a TCA-independent manner by acting as a cofactor for dioxygenases, controlling gene expression, DNA methylation, and DNA damage reactivity [53]. Similarly to glutamine, alanine is also required for metabolic homeostasis in PDAC and is derived from pancreatic stellate cells (PSCs) [54]. Several studies have investigated the unidirectional channeling of alanine between PSCs and PDAC [54], [55]. SLC38A2 activity facilitates alanine uptake, although other transporters have been identified, including SLC1A4 [54]. PDAC cells also express the mitochondrial isoform of glutamic-pyruvic transaminase ALT2 for *de novo* synthesis and alanine utilization. The ratio between aspartate transaminase AST and alanine aminotransferase ALT was used to predict poor prognosis and response to gemcitabine/nab-paclitaxel treatment in PDAC patients [56]. In co- injection xenograft models, the beneficial support provided by stellate cells was disrupted by targeting SLC38A2, causing significant tumor regression in PDAC and affecting cytosolic alanine internalization and concentration [54]. PDAC can also use proline as a fuel source, and this energy comes from collagen that is largely found in the ECM [57]. Proline degradation by the mitochondrial enzyme PRODH1 plays as

an active factor in PDAC cell proliferation both *in vitro* and *in vivo* [57], indicating that ECM is an important nutrient reservoir for cancer cell metabolic flexibility. Some context-specific metabolic mechanisms have also been described for PDAC, such as the TP53-mediated overexpression of SLC1A3, an $Na^+/K^+/H^+$-dependent aspartate/glutamate transporter, which enables the aspartate metabolism to maintain cancer cell survival and tumor growth under conditions of glutamine starvation [58]. By perturbing glutamine metabolism, redox homeostasis proteins are deregulated, leading to reactive oxygen species ROS accumulation, which then leads to a cellular redox imbalance facilitating PDAC cell apoptosis [59]. Pharmacological and genetic targeting of nicotinamide phosphoribosyltransferase (Nampt), a key redox enzyme, inhibited cell growth and survival of PDAC cells *in vitro* and *in vivo* [60]. Other findings link amino acids with cell fate. KRAS-driven PDAC mouse models was less responsive to depletion of serine and glycine [61]. Cysteine depletion induced ferroptosis in *KRAS/TP53* mutant pancreatic tumors in mice, and the disruption of amino acid pathways was able to enhance gemcitabine chemosensitivity in drug-resistant PDAC [62], [59]. Ferroptotic damage can result in the of release damage-associated molecular pattern molecules, which can lead to inflammation [63].

3. Fatty Acids Contribute to PDAC Progression

Epidemiological studies correlated PDAC with dyslipidemia [64], showing an altered biosynthesis of cholesterol and other lipids in murine PDAC cells [65], [66], [67], [68]. Lipogenic enzymes are frequently overexpressed in PDAC, supporting their potential contribution to tumor growth [69]. Alanine from PSCs can be taken up by PDAC cells and used for FA biosynthesis. Serum FA synthase (FASN) levels are in fact generally higher in PDAC patients [70] as a result of SREBP1 activity [71] and are associated with lower survival than in patients with low FASN expression and with poor response to gemcitabine [72], [73]. Once again, driver mutations in KRAS and loss-of-function in TP53 reprogram metabolism, accelerating cholesterol biosynthesis and uptake [1], mediating metabolic plasticity via SREBP1-dependent regulation of transforming growth factor-β expression involved in PDAC differentiation. Oncogenic KRAS regulates hormone-sensitive lipase (HSL) to control metabolism by regulating lipid storage and utilization (specifically through suppression of HSL expression), leading to lipid droplet (LD) accumulation and priming tumor cells for invasion [74]. Perilipins constitute the major proteins resident on LD surface controlling intracellular lipid homeostasis [75], [76]. Perilipin 2 (PLIN2) was found overexpressed in a cohort of 181 PDAC patients [77] and was associated with poor MFS, DFS, and OS rates as well as with poor prognosis. Further investigations using an in vivo mouse model showed that exposure of pancreatic β cells to fatty acids stimulated PLIN2 expression, impacting on cellular stress, whereas its ablation prevented fatty acid-induced TG accumulation [76], mitigating stress and leading to a significant improvement of hyperglycemia [78]. Notably, PLIN2 is expressed in other cell types such as monocytes and macrophages [79], where its expression was positively correlated with LGALS9 in PDAC; this protein converts polarized macrophages into an M2 phenotype, leading to the inhibited secretion of T cell cytokines [80]. These findings suggest that PLIN2 might participate in immunomodulatory effects by regulating tumor-associated macrophages in the tumor microenvironment [81]. A high fat diet was able to ameliorate mutated Kras activity, increasing fibrosis and enhancing PDAC progression in a mouse model [82], and a recent study with in vivo mouse model showed a causal and positive corrrelation between obesity and early PDAC progression, identifying altered beta cell expression of cholecystokinin (Cck) in response to obesity defining islet

Cck as *a* promoter in oncogenic Kras-driven PDAC [83]. LDs are recognized as important regulators in cancer; these dynamic intracellular organelles are used for cellular storage of lipids such as triacylglycerol and cholesterol ester [84]. Lipids can thus be catabolized by lipolysis via lipases to liberate free FAs [85], causing increased FA oxidation and oxidative metabolism, which drives tumor cell invasion. Low-density lipoprotein receptor (LDL-R) is highly expressed in PDAC and is associated with increased PDAC recurrence [86]. LDL-R increases cholesterol uptake, while its inhibition reduces proliferation, affecting ERK1/2 survival pathway, and sensitizes PDAC cells to chemotherapeutic drugs, favoring tumor regression [86]. Interestingly, mutated KRAS is able to control the sequestration of extracellular unsaturated FAs [87]. ACSL3 activity, a protein coding gene for a member of Acyl-CoA synthetase long chain family, has been linked to KRAS-mutated tumors [88] and associated with the retention of extracellular unsaturated FAs by converting them into esters that remain confined in PDAC cells [89], [90]. Serum lipid depletion or ACSL3 inhibition decreased tumor cell proliferation, provoking a rebound effect due to lipid restriction that was balanced by increased autophagic flux, in both in vitro and in vivo models [91]. Notably, combining lipid depletion with autophagy inhibitors induced the most potent effect, with arrest of PDAC proliferation and increased apoptosis [91]. Recently, metabolomic profiles clarified key aspects of the metabolic signature of pancreatic cancer stem cells (PCSCs) originating from PDAC cells, revealing a fundamental role for pyruvate-malate cycle and lipid metabolism in their survival [92]. While lipidomic analysis suggested a strong induction of long chain FAs and accumulation of LDs mediated by ELOVL5, a fatty acid elongase, other data highlighted cardiolipin acyl-chain composition as pivotal in PCSCs [93]. Changes in cardiolipin composition have an impact on enzymes involved in the respiratory process and integrity of the inner membrane [94], [95], indicating that cardiolipin plays a critical role in oxidative phosphorylation. A comprehensive investigation on serum lipids of 830 PDAC samples by mass spectrometric determination revealed statistically significant differences between PDAC patients and healthy controls [96]. While a lysophosphatidylcholine LPC 18:2 was positively correlated with survival, Cer 36:1, Cer 38:1, Cer 42:2, PC 32:0, PC O-38:5, and SM 42:2 were inversely correlated, suggesting their potential role as prognostic biomarkers. Other data in PDAC tissues by MALDI-MSI analyses indicated that LPC (16:0, 18:1), as reported for other LPCs [97], [98], and DAG 36:2 were decreased, while PC 32:0, SM d36:1, and SM d42:3 were increased [99]. Glycerophospholipid and sphingolipid metabolism pathways were also found dysregulated in PDAC [99]. About lipid saturation degree, polyunsaturated phosphatidylcholines were reduced in serum of PDAC [100] it is tempting to speculate that this altered profile might reflect apoptotic resistance in PDAC, given that polyunsaturated FAs, via peroxidation, act as substrates for ferroptosis in cell membranes [101], [102].

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