The Intricate Metabolism of Pancreatic Cancers

Felipe Camelo and Anne Le

Key Points

- Oncogenic *KRAS* regulates glucose and glutamine metabolism in pancreatic cancer cells.
- MUC1 overexpression leads to increased glucose metabolism.
- p53 functions predict the sensitivity of pancreatic cancer tumors to glycolytic inhibition.
- Targeting alpha-ketoglutarate dehydrogenase function by CPI-613 to slow mitochondrial metabolism.
- The antidiabetic drug, metformin, targets pancreatic cancer stem cells.
- Combined therapy is used to target pancreatic metabolism heterogeneity.

Keywords Pancreatic ductal adenocarcinoma · *KRAS* mutation · Glucose metabolism · Glutamine metabolism · Combined therapy

Abbreviations

ASP	Aspartate
EGFR	Epidermal growth factor receptor
GLS	Glutaminase
GLUD1	Glutamate dehydrogenase 1

F. Camelo
Department of Pathology, Johns Hopkins University School of Medicine,
Baltimore, MD, USA

A. Le (✉)
Department of Pathology and Oncology, Johns Hopkins University School of Medicine,
Baltimore, MD, USA
e-mail: annele@jhmi.edu

GLUT   Glucose transporter
GOT1   Glutamic-oxaloacetic transaminase 1
HIF-1α   Hypoxia-inducible factor 1-alpha
HK2   Hexokinase 2
KRAS   Kirsten rat sarcoma viral oncogene homolog
LDH   Lactate dehydrogenase
MCT   Monocarboxylate transporter
OAA   Oxaloacetate
PDAC   Pancreatic ductal adenocarcinoma
PFK1   Phosphofructokinase 1
TCA   Tricarboxylic acid cycle

Introduction

Currently, approximately 95% of pancreatic cancers are pancreatic ductal adenocarcinoma (PDAC), which is the most aggressive form and the fourth leading cause of cancer death with extremely poor prognosis [1]. Poor prognosis is primarily attributed to the late diagnosis of the disease when patients are no longer candidates for surgical resection [2]. Cancer cells are dependent on the oncogenes that allow them to proliferate limitlessly. Thus, targeting the expression of known oncogenes in pancreatic cancer has been shown to lead to more effective treatment [3]. This chapter will discuss the complexity of metabolic features in pancreatic cancers. To be able to fully comprehend the heterogeneous nature of cancer metabolism, we need to take into account the close relationship between cancer metabolism and genetics. Gene expression varies tremendously, not only among different types of cancers, but also within the same type of cancer among different patients. Cancer metabolism heterogeneity is often prompted and perpetuated not only by genetic mutations in oncogenes and tumor suppressor genes but also by the innate diversity of the tumor microenvironment. Much effort has been focused on elucidating the genetic alterations that correlate with disease progression and treatment response [4]. However, the precise mechanism by which tumor metabolism contributes to cancer growth, survival, mobility, and aggressiveness represents a functional readout of tumor progression.

1   Oncogenic *KRAS* Regulates Metabolism in Pancreatic Cancer Cells (Fig. 1)

1.1   *Oncogenic KRAS Regulates Glutamine Metabolism*

A cancer cell's specific metabolic adaptations in nutrient uptake and biosynthesis have been linked to a particular genetic mutation. The *KRAS* (Kirsten rat sarcoma) oncogene homolog is a known regulator of glutamine metabolism among other
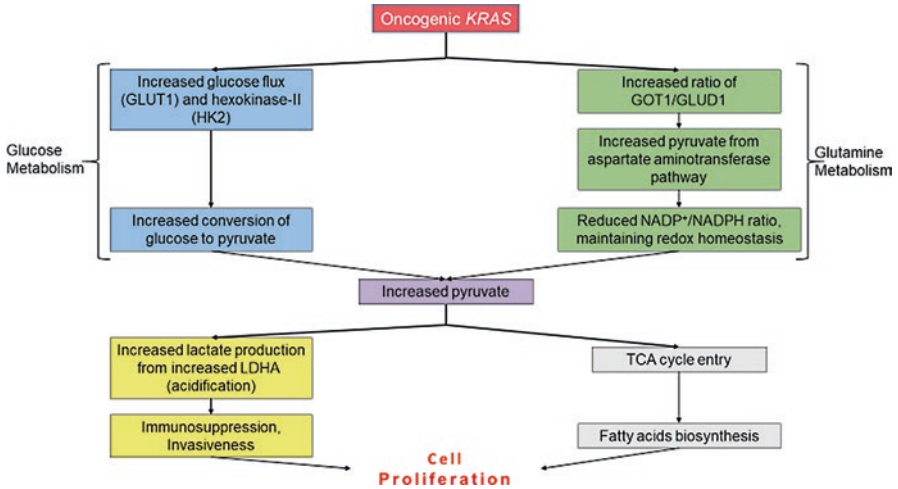
Fig. 1 Oncogenic KRAS regulates glutamine and glucose metabolism in PDAC

intermediary metabolic pathways that renders cancer cells addicted to glutamine [5–7]. A range of mutations in the *KRAS* oncogene occurs in over 90% of PDAC [8, 9].

Normally, glutamate feeds into the TCA cycle after being converted to alpha-ketoglutarate in the mitochondrion via glutamate dehydrogenase 1 (GLUD1). A study by Son et al. showed that KRAS regulated the reprogramming of glutamine metabolism through transcriptional regulation of key metabolic enzymes of transaminase reactions which, in turn, determine PDAC tumor growth. Notably, they concluded that PDAC cells greatly depend on these reactions for redox homeostasis. Given that this pathway is nonessential in normal cells, the unique importance of this pathway in PDAC suggests novel approaches to therapy in treating PDAC [6]. *KRAS* mutation led to the reprogramming of glutamine metabolism, which was partially due to increased aspartate aminotransferase or Glutamic-oxaloacetic transaminase 1 (GOT1) expression and decreased GLUD1 expression. The change in the ratio of expression of GOT1 and GLUD1 shunts glutamine flux through the aspartate aminotransferase pathway. Furthermore, they demonstrated that GOT knockdown failed to impair growth in several normal cell lines. According to Lyssiotis et al., the observation that the glutamine metabolism pathway is downstream of mutant *KRAS* serves as an explanation for the distinct glutamine dependency of pancreatic cancer. Not only do their results yield novel targets for pancreatic cancer therapy, but they also suggest that inhibiting glutamine metabolism in pancreatic cancer therapies may synergize with therapies that increase ROS [7].

1.2   Oncogenic KRAS Regulates Glucose Metabolism

The *KRAS* oncogene is also known to contribute to the glucose metabolism in pancreatic cancer cells via upregulation of glucose uptake and diversion of glucose into the hexosamine biosynthesis pathways [10]. Oncogenic *KRAS* controls the diversion of glycolytic intermediates into ribose biosynthesis pathways via upregulation of the non-oxidative pentose phosphate pathway (PPP), a pathway that is fundamental to nucleic acid synthesis and thus cancer cell proliferation [10]. Expression of GLUT1 (glucose transporter-1), hexokinase-II (HK2), and LDHA that catalyzes the reaction of pyruvate to lactate is greatly enhanced by *KRAS* in pancreatic tumor cells [10]. Subsequently, glycolytic flux, the production of lactate from glucose, was high in *KRAS*-mutant tumors. It is of note that these alterations are not nearly as pronounced in the stromal cells of these tumors which are able to uptake the lactate generated by tumor cells and use pyruvate dehydrogenase (PDH) to convert the lactate back to pyruvate in order to fuel the TCA cycle [11, 12]. Yun et al. found that cells with mutated *KRAS* undergo the Warburg effect and survive in low-glucose environments compared to cells with wild-type *KRAS* due to the fact that *KRAS* upregulated GLUT1 [13]. This suggests that *KRAS* mutation is involved in the altering of a cancer cell's bioenergetics that is seen in most PDAC tumor cells, which take advantage of altered metabolic pathways to successfully proliferate and grow.

2   Other Alternative Metabolisms in Pancreatic Cancer

2.1   MUC1 Overexpression Leads to Increased Glucose Metabolism

A study by Chaika et al. revealed that the overexpression of transmembrane protein MUC1 led to elevated glucose metabolism and related activities, such as increased glucose uptake and lactate production resulting from increases in GLUT1 expression and LDHA expression, respectively. These metabolic effects are particularly pronounced under hypoxic conditions, which are associated with the stabilization of hypoxia-inducible factor 1-alpha (HIF-1α), a transcription factor for many genes involved in regulating glucose uptake, through the overexpression of MUC1 [14]. Pancreatic cancer cells that do not overexpress MUC1 have a reduction in lactate and glycolytic intermediates. Overall, the overexpression of MUC1 is capable of influencing glucose metabolism, the elevation of amino acid metabolism, and the TCA cycle, all of which are important in the biosynthesis of cellular building blocks, and thus tumorigenesis. The signaling pathway associated between MUC1 and HIF-1α plays an important role in the facilitation of tumor growth and metastasis, serving as a potential target for manipulation in the treatment of diseases reliant upon these proteins [14].

2.2 p53 Functions Predict the Sensitivity of Pancreatic Cancer Tumors to Glycolytic Inhibition

The heterogeneity of metabolic alterations within the same cancer types is best illustrated by a recent study by Rajeshkumar et al. They showed that PDAC's sensitivity to the same metabolic inhibition could vary drastically from one tumor to another, depending on the specific tumor's genetic status and unique metabolic phenotype [15]. More specifically, they uncovered that responses to LDHA inhibition by the small-molecule FX11 were determined by a tumor's p53 status, a tumor suppressor gene that is largely inactivated in many cancers [16]. Within the same PDAC type, tumors with wild-type TP53 demonstrated resistance to FX11, while those with mutant TP53 exhibited sensitivity in the form of increased apoptosis, reduced proliferation, and attenuated tumor growth. Their data show that FX11 specifically reduces pyruvate to lactate conversion by LDHA *only* in the *TP53*-mutant tumor, suggesting LDHA inhibition as a possible therapeutic target to reduce TP53-mutant tumor growth. Resistance in *TP53*-WT tumors is thought to result from reduced dependence on glucose, as corroborated by their data showing higher levels of TIGAR, a p53-inducible protein that lowers glycolytic flux [17]. This study supports not only growing evidence for variable metabolic phenotypes across cancer types but also within cancers of the same type. From a clinical perspective, this insight emphasizes the importance of metabolic phenotypes in pancreatic cancer sub-characterization in order to pair drug therapies according to phenotypic sensitivity for a more selective and personalized treatment.

3 Suggested Therapy (Fig. 2)

The *KRAS* gene may be a solution to this type of disease since *KRAS* appears to have a prominent role in the metabolic rewiring of PDAC tumors and plays critical roles in PDAC pathogenesis [9]. While oncogenic *KRAS* alters the PDAC cell's metabolism, it requires the cancer cell to become dependent on the oncogenic *KRAS* to continue proliferation [18]. This is known as oncogene addiction, in which the cancer cell becomes dependent on the activity of the oncogene for survival and proliferation [3]. Since *KRAS* mutations are found in a majority of PDAC cancer cells and *KRAS* regulates cancer cell's metabolism, targeting these regulations for cancer therapy is an approach that researchers are taking [18].

Fig. 2 Overview of
therapeutic options
targeting pancreatic cancer
metabolism
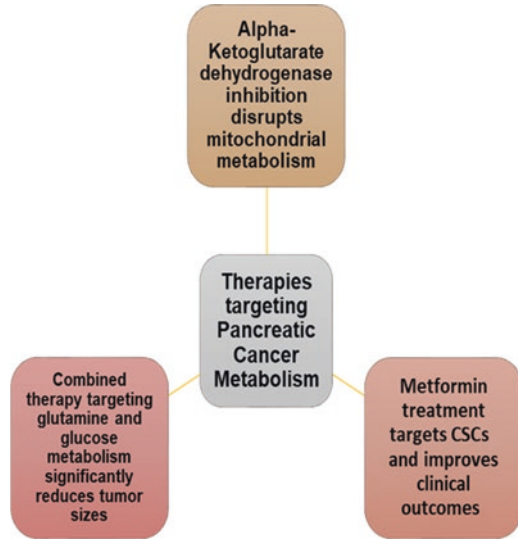
3.1 Alpha-Ketoglutarate Dehydrogenase Function by CPI-613 to Slow Mitochondrial Metabolism

Drugs have been developed to target mitochondrial metabolism in cancers [18]. One of these drugs is CPI-613, an inhibitor of cancer-specific mitochondrial energy metabolism. The drug causes tumor cell apoptosis, necrosis, and autophagy by selectively targeting alterations in mitochondrial enzyme activities and redox status [19]. CPI-613 is a small molecule that attacks alpha-ketoglutarate dehydrogenase in tumor cells through a redox process [20]. The drug is known to simultaneously attack multiple essential components of tumor cell regulation [20]. However, the exact mechanism is not well understood. CPI-613 has been recognized to be effective against various types of cancers [21], including patients with metastatic pancreatic cancer [19]. CPI-613 used in combination with modified FOLFIRINOX (mFOLFIRINOX) in patients with metastatic pancreatic cancer demonstrated better survival, but since this phase I study was not designed to determine the efficacy of adding CPI-613 to mFOLFIRINOX, the results should be interpreted with caution. Nevertheless, Alistar et al. have obtained encouraging results from the phase I studies and are currently performing a randomized phase II trial to compare FOLFIRINOX against mFOLFIRINOX with CPI-613. These results suggest that targeting mitochondrial metabolism holds enormous potential in combating pancreatic cancer.

3.2 Antidiabetic Drug, Metformin, Targets Pancreatic Cancer Stem Cells

Recent studies have shown that tumorigenic cancer stem cells (CSCs), a highly chemoresistant subclass of PDAC, are strongly dependent on oxidative metabolism [22, 23]. Retrospective analysis showed that oral administration of metformin in patients with type 2 diabetes was associated with reduced risk of developing PDAC [24] along with a better outcome for patients that had established PDAC [25]. More recently, it has been discovered that metformin targets pancreatic CSCs but not the differentiated progenies (non-CSCs) [22]. *KRAS* targeting has resulted in tumor shrinkage but fails to kill all the CSCs [26]. Viale et al. established that dormant tumor cells that survived oncogene ablation were shown to have high sensitivity to oxidative phosphorylation inhibitors [26]. Lonardo et al. uncovered that metformin uniformly reduced ATP levels in adherent cells and sphere cells from CSCs, but not in non-CSCs [23]. Although the mechanism for metformin in CSCs is largely unknown, what is known is that metformin slowly accumulates in the mitochondria and directly inhibits complex 1 (NADH dehydrogenase) in the electron transport chain, affecting oxidative phosphorylation [23]. Therefore, a potentially strong therapeutic strategy to manage pancreatic cancer is the combined targeting of the *KRAS* pathway and mitochondrial respiration [26].

3.3 Combined Therapy to Target Pancreatic Metabolism Heterogeneity

Combination therapy to target multiple metabolic pathways in pancreatic cancer has been demonstrated as a favorable therapeutic solution. Elgogary et al. found that targeting glutamine metabolism using the glutaminase inhibitor bis-2-(5-phenylacetamido-1,2,4-thiadiazol-2-yl)ethyl sulfide (BPTES) encapsulated in nanoparticles effectively shrinks pancreatic cancer tumor size and slows proliferation [27]. They also found, using metabolomics technologies, that the tumor cells remaining after glutaminase inhibition were dependent on glycolysis and glycogen synthesis. Elgogary et al. continued the study by adding both BPTES nanoparticles and metformin to target both glutamine and glucose metabolisms in pancreatic cancer cells. They discovered that the combined therapy provided enhanced efficacy that inhibited tumor growth significantly more compared to the single treatment of BPTES or metformin alone. This highlights the fact that there is great heterogeneity in pancreatic cell metabolism since targeting only glutamine metabolism did not kill all the pancreatic cancer cells, but targeting both glutamine and glucose metabolisms reduced the tumor growth of the cells with considerably larger efficacy than targeting either glutamine or glucose metabolism alone. This has been observed in pancreatic cancer cells, but more clinical trials must be done in order to see if combination therapy can assist in pancreatic cancer patient survival.
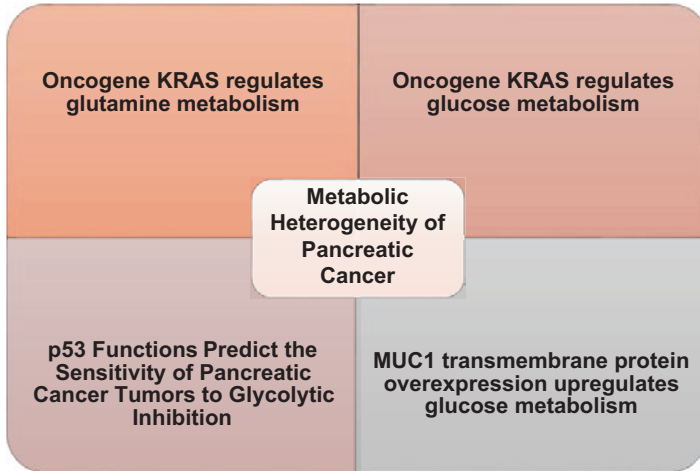
Fig. 3 Overview of pancreatic cancer metabolic heterogeneity

Conclusion

Pancreatic ductal adenocarcinoma is the fourth leading cause of cancer death in the United States and is expected to be the second largest by 2030 [28, 29]. The deadliness of this disease can be attributed to its metabolic heterogeneity which developed through cancerous evolution (Fig. 3). With that in mind, the investigation of PDAC within the past few years has been exponentially increasing with improved technology and research methods that allow us to understand these intricate mechanisms better. Exploration of more aspects of a pancreatic cell enables scientists and clinicians to better target multiple facets of a pancreatic cell, resulting in more effective therapeutic methods.

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