Interplays of glucose metabolism and KRAS mutation in pancreatic ductal adenocarcinoma

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Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive and deadliest cancer worldwide. The primary reasons for this are the lack of early detection methods and targeted therapy. Emerging evidence highlights the metabolic addiction of cancer cells as a potential target to combat PDAC. Oncogenic mutations of KRAS are the most common triggers that drive glucose uptake and utilization via metabolic reprogramming to support PDAC growth. Conversely, high glucose levels in the pancreatic microenvironment trigger genome instability and de novo mutations, including KRASG12D, in pancreatic cells through metabolic reprogramming. Here, we review convergent and diverse metabolic networks related to oncogenic KRAS mutations between PDAC initiation and progression, emphasizing the interplay among oncogenic mutations, glucose metabolic reprogramming, and the tumor microenvironment. Recognizing cancer-related glucose metabolism will provide a better strategy to prevent and treat the high risk PDAC population.

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FACTS

● Although the association between diabetes and PDAC has been revealed, whether diabetes is a predisposing factor or an early manifestation of malignancy remains unsettled.
● One of the potential therapeutic strategies for PDAC is to target the metabolic addiction of cancer cells.
● KRAS proto-oncogene mutations shut glycolysis hexosamine biosynthesis and pentose phosphate pathways.
● High glucose initiates genome instability and de novo mutations, including KRASG12D, in nontumorigenic pancreatic cells.
● Alternation of O-linked-N-acetylglucosaminylation changes cellular and physiological homeostasis fueling PDAC initiation and progression.

PDAC: A GROWING SILENT KILLER

Pancreatic ductal adenocarcinoma (PDAC), the seventh leading cause of cancer-related death worldwide in 2020, accounts for ~95% of all pancreatic cancers as well as 4.9% and 4.5% of estimated age-standardized incidence and mortality rates, respectively, with almost as many deaths as the number of cases [1]. PDAC will foreseeably become the second leading cause of cancer-related deaths by 2026 [2], with an ~11.5% 5-year relative survival rate in the United States [3]. Due to the lack of an early detection method and effective therapeutics, diagnosis generally occurs at an advanced stage, when patients already have locoregional extensions or metastases that render surgical resection ineffective [4]. PDAC stems from abnormal acinar-to-ductal metaplasia (ADM) and pancreatic intraepithelial neoplasia (PanIN) of grades I–III [5]. One of the potential therapeutic strategies for PDAC is to target the unique nutrient availability and utilization in cancer cells [6, 7]. Significant advances have been made in understanding metabolic adaptations to KRAS hyperactivation. Efforts are ongoing to design metabolism-targeted diagnostic and therapeutic strategies. Nevertheless, the most potent strategy should aim to prevent PDAC initiation and enhance early detection.

Considering genetic and personal risk factors [8], novel findings have suggested aberrant metabolites not only as promoters [9] but also as initiators [10] for PDAC, and common metabolic reprogramming patterns have gained a hotspot for prevention or early detection [11]. This review provides a synopsis of metabolic dependence supporting oncogenic mutation-driven PDAC progression, emphasizing that aberrant nutrient availability and utilization may also cause oncogenic mutations. This review also offers an outlook of potential targets for PDAC therapeutics, prevention, or early detection.

KRAS MUTATION AND METABOLIC ALTERATIONS

Cancer cells become dependent on activated oncogenes or their downstream metabolic processes for survival and proliferation [12]. Inhibiting oncogenes or their downstream mediators is expected to
be lethal to metabolically addicted cells without harming normal cells. Advances include dependence on poly(ADP-ribose) polymerase activity in the context of BRCA deficiency [13, 14]. The somatic mutation of oncogenic KRAS is the most recognized genetic alteration and is thus the most attractive drug target in PDAC [15, 16]. Mutant KRAS increases the expression of glucose transporter 1 (GLUT1) and rate-limiting glycolytic enzymes, including hexokinases, phosphofructokinase 1 (PFK1), and lactate dehydrogenase A (LDHA), promoting glycolytic activity and increasing lactate production [17, 18]. By upregulating these enzymes, mutant KRAS triggers the shunting of glycolytic intermediates into the hexosamine biosynthesis pathway (HBP) to generate UDP-N-acetylglucosamine (UDP-GlcNAc) for glucocorticoid, glycolipid, proteoglycan, and glycosylphosphatidylinositol anchor biosynthesis in cancer cells [5, 19]. The shunting of glycolytic intermediates into the nonoxidative arm of the pentose phosphate pathway (PPP) generates the ribose 5-phosphate necessary for nucleic acid biosynthesis and nicotinamide adenine nucleotide phosphate (NADPH) for regenerating glutathione (GSH) from oxidized GSH (GSSG) to support ROS scavenging for redox balance. GSH biosynthesis depends on glutamine. While most cells convert glutamine-derived glutamate to glutamine. While most cells convert glutamine-derived glutamate to glutamine. While most cells convert glutamine-derived glutamate to glutamine. While most cells convert glutamine-derived glutamate to glutamine. While most cells convert glutamine-derived glutamate to glutamine. While most cells convert glutamine-derived glutamate to glutamine. While most cells convert glutamine-derived glutamate to glutamine. While most cells convert glutamine-derived glutamate to glutamine. While most cells convert glutamine-derived glutamate to glutamine. While most cells convert glutamine-derived glutamate to glutamine. While most cells convert glutamine-derived glutamate to glutamine. While most cells convert glutamine-derived glutamate to glutamine. While most cells convert glutamine-derived glutamate to glutamine. While most cells convert glutamine-derived glutamate to glutamine. While most cells convert glutamine-derived glutamate to glutamine. While most cells convert glutamine-derived glutamate to glutamine. While most cells convert glutamine-derived glutamate to glutamine.
addition of N-acetylglucosamine (GlcNAc) moieties from UDP-GlcNAc to serine and threonine residues of proteins. The addition and removal of O-GlcNAc rely on O-GlcNAc transferase (OGT), which adds UDP-GlcNAc to target proteins, and O-GlcNAcase (OGA), which removes O-GlcNAc from O-GlcNAcylated proteins [63]. The generation of UDP-GlcNAc is not only for O-GlcNAcylation but also for O-glycosylation and N-glycosylation of proteins to maintain cellular survival under stress [63]. As a nutrient sensor, HBP is essential for amino sugar biosynthesis by integrating core metabolic intermediates from glycolysis, fatty acids, amino acids, and nucleotide metabolism [64, 65]. However, either cancer cells under glucose deprivation, hypoxia, or oncogenic KRAS mutation [8] or nontumorigenic pancreatic cells under high glucose levels [10] cause hyper-O-GlcNAcylation of cellular proteins, challenging the regulation of O-GlcNAcylation via the versatile UDP-GlcNAc.

Metabolic reprogramming may be dynamic, unsynchronized, and coordinated with neighboring cells in an organism in response to extracellular and intracellular stresses. Several O-GlcNAcylation targets related to PDAC metabolism and progression, such as notch receptor 1 promoting cancer development [66], SRY-box transcription factor 2 regulating self-renewal [67], sirtuin 7 (SIRT7) triggering cancer progression by blocking the SIRT7-proteasome activator subunit 3 (PAME3) interaction [68], and nuclear factor kappa B modulating cancer-associated inflammation [69], have been reported. Although hyper-O-GlcNAcylation of insulin receptor substrate 1 and AKT serine/threonine kinase 2 inhibits their phosphorylation and induces insulin resistance in peripheral cells [70], the corresponding regulation of endocrine and exocrine secretion from the pancreas remains unclear. Protein O-GlcNAcylation in response to high glucose-driven metabolic reprogramming may potentially have multiple targets beyond PFK1 and RRM1 in nontumorigenic pancreatic cells [10]. The precise control and crucial targets of O-GlcNAcylation and how O-GlcNAcylation helps adapt and maintain homeostasis in a specific organ under stress remain to be explored. The safe use of glucosamines, the UDP-GlcNAc precursor, as a dietary supplement for osteoarthritis under variable O-GlcNAcylation due to UDP-GlcNAc imbalance or OGT/OGA dysregulation has to be reconsidered [62, 71].

Thus, unlike glycated proteins such as carbohydrate antigen 19-9 (CA19-9) and hemoglobin A1c (Hb A1c) with mutually correlated levels [72], glycosylated proteins that help cancer cells adapt to stress and malignant phenotypes could serve as potential diagnostic and therapeutic targets [63, 71].
Potential factors regulating HBP in a high glucose status

HBP is essential for versatile UDP-GlcNAc synthesis. Regulations of enzymes critical for HBP and controlling high glucose-induced protein O-GlcNAcylation should be discussed. PFK1, a 340 kDa heterotetrameric allosteric enzyme composed of PFKL, PFKM, and PFKP, works with a concerted symmetric transition from an enzymatically inactive T-state to the active R-state and can be dissociated into inactive dimers and monomers [73]. Increased PFK activity may help pancreatic cells maintain their survival advantage during adaptation to the poor oxygen and nutrient supply microenvironment [18]. In contrast, high glucose-induced O-GlcNAcylation inactivates PFK1 and RRM1 and subsequently inhibits glycolysis and dNTP generation, respectively, resulting in high-frequency DNA damage, specifically in pancreatic cells [10]. Modulation of PFK activity during adaptation or hyperproliferation may result from different posttranslational modifications and/or subunit assembly, which warrants further investigation.

Another crucial target for rewiring glycolysis in the HBP is GFTA. GFTA, the first and rate-limiting enzyme of HBP, catalyzes glucosamine 6-phosphate by integrating glucose and glutamine metabolism. High levels of GFTA predict a poor prognosis in patients with PDAC [74]. GFTA1 depletion diminished high glucose-induced DNA damage and colony formation in pancreatic cells [10]. GFTA2 upregulation positively correlates with hyaluronic acid and nutrient supply microenvironment [18]. In contrast, high glucose-induced O-GlcNAcylation inactivates PFK1 and RRM1 and subsequently inhibits glycolysis and dNTP generation, respectively, resulting in high-frequency DNA damage, specifically in pancreatic cells [10].

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Since epigenetics plays a key role in regulating gene expression in different tissues and cell types [76], its contribution to the causal relationship of metabolite preference toward lower PFK activity in pancreatic cells is of great interest. Furthermore, ER stress may trigger HBP overactivation. The unfolded protein response (UPR)-HBP axis is partially triggered via GFTA1, a direct transcriptional target of a spliced form of X-box binding protein 1 (XBP1s), to protect cells under stress [77]. XBP1s also promotes pro-survival signaling during acinar cell differentiation [78]. In addition, ER stress sensors such as glutathione peroxidase 7 relieve ER oxidative stress by promoting 78 kDa glucose-regulated protein chaperone activity [79], linking the stress sensor to HBP activity.

Glucosamine-phosphate N-acetyltransferase 1 (GNPNAT1) is a key enzyme associated with glucose and fatty acid catabolism and UDP-GlcNAc biosynthesis. Although GNPNAT1 overexpression is associated with poor survival of patients with PDAC, the mechanisms underlying the link remain to be explored (TGCA dataset, unpublished results). Overexpression of phosphoacetylglucosamine mutase (PAM3, a phospho-N-acetylglucosamine mutase) has been linked to gemcitabine resistance. The PAM3 inhibitor FR054 synergizes with gemcitabine to suppress PDAC growth by promoting the UPR and inhibiting EGFR-AKT signaling [80]. The expression of UDP-N-acetylglucosamine phosphorlyase (UAP1), GlcNAc kinase (GNAK), OGT, or OGA was not associated with poor survival of PDAC (TGCA dataset, unpublished results). These results suggest that multiple intertwined factors may connect the regulation of HBP pathway.

**NUTRIENT SHARING AND COMPETITION: HOW KRAS-MUTATED CELLS PREVAIL IN COMPETITION**

**Stress from the pancreatic cell microenvironment**

The TME of PDAC is composed mainly of stroma with primary fibroblasts and immune cells [31, 81] and is a physical and oxidative stress source. Fibroblast-induced cell dysfunction may occur through extracellular matrix (ECM)-induced physical destruction, resulting in pancreatic fibrosis [82] and PDAC progression [83]. Those tissue injuries lead fibroblasts to produce extensive ECM to increase interstitial stresses [84]. The stresses in PDAC may exceed ten times of those observed in a normal pancreas [85, 86]. Although stromal components create a metabolic niche for cancer cells to maintain tumor survival, they might also restrain cancer progression [87–90].

Oxidative stress from TME can be resulted from nutrient imbalances. Consistent with this notion, metabolic imbalance-induced genomic instability and DNA damage may involve oxidative stress and DDR inefficiency. Using nucleotide supplements to reverse high glucose-induced DNA damage supports this potential [10, 62]. Interestingly, similar example is that BRCA2 DNA repair-associated (BRCA2)-deficient cells also experience endogenous oxidative stress-blocked mtDNA replication and stability, which could be ameliorated by the ROS scavenger N-acetylcysteine [48]. The redox shuttle enables NADPH transfer from the cytosol to the mitochondria to support cellular

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**Fig. 2** The de novo hexosamine biosynthetic pathway (HBP) and GlcNAc salvage pathway integrate metabolic status from core metabolism intermediates, including glycolysis, fatty acid, amino acid and nucleotide metabolism, to generate uridine diphosphate-N-acetylglucosamine (UDP-GlcNAc). Approximately 2–5% of cellular glucose enters the HBP to generate the end product UDP-GlcNAc. Glutamine:fructose-6-phosphate amidotransferase (GFAT) is the rate-limiting enzyme for the HBP. O-GlcNAc transferase (OGT) adds UDP-GlcNAc to target protein serine and threonine residues, and O-GlcNAcase (OGA) removes O-GlcNAc from O-GlcNAcylated proteins. The balance between the enzyme activities of phosphofructokinase (PFK) and GFAT through regulating GFAT may be crucial to direct the pathways. G6P glucose 6-phosphate, F6P fructose 6-phosphate, FBP fructose 1,6-phosphate, GlcN6P glucosamine-6-phosphate, GlcNAc6P N-acetylglucosamine-6-phosphate, GlcNAc1P N-acetylgulcosamine-1-phosphate, GAT acetyl-CoA:D-glucosamine-6-phosphate N-acetyltransferase, AGM phosphor-N-acetylglucosamine mutase, AGK GlcNAc kinase. The graph was created with BioRender.com.
homeostasis. However, a severely inefficient DDR from the challenge of metabolite imbalance may lead to cell death. BCL-2 family proteins control cell death or differentiation primarily through the irreversible release of intermembrane space proteins, caspase activation, and apoptosis through direct interaction-regulated mitochondrial outer membrane permeabilization (MOMP). Aberrant oxidative stress alters the affinities and relative abundance of BCL-2 family proteins, affecting BCL-2 family protein interactions [46]. However, no consistent trends in ROS levels have been detected between two nontumorigenic pancreatic cell lines upon high glucose-induced DNA damage [10]. Other cellular antioxidants, including superoxide dismutases, glutathione S-transferases, glutathione peroxidases, and periaxin, may also protect against ROS-induced cell death, partly through nuclear factor erythroid 2–related factor 2 [91]. Personalized nutrient guidelines for restraining specific tumor growth will be an interesting subject to explore.

**PDAC associated microbiome: an enigma**

The microbiota may be another risk factor for PDAC. Differences in oral, gut, and pancreatic microbiota have been reported among patients with PDAC. Oral microbiota dysbiosis may contribute to PDAC pathogenesis [92]. PDAC pathogenesis has been reported to link to an increased abundance of periodontal disease-associated *Pseudomonas gingivalis* and *Fusobacterium* sp. but reduced abundances of *Neisseria elongata* and *Streptococcus mitis* [93]. High levels of plasma antibodies against *P. gingivalis* have been correlated with a reduced risk of PDAC [94].

The interaction between microbiota and host, nutrient/drug efficacy, and toxicity directly alter or indirectly modify host physiology and pharmacodynamics. Current gut microbiome-cancer associations are witnessed in bacteria causing tumor progression and bacteria modulating antitumor immune responses [95, 96], which are partially dependent on comtabolites derived from the host and microbiota, such as short-chain fatty acids, bile acids, and indole derivatives, which are greatly influenced by nutrients [97]. For gut dysbiosis, an increased abundance of Bacteroidetes but a reduced abundance of Firmicutes in patients with PDAC have been found [98]. A lower α-diversity in the gut microbiome in patients with PDAC was detected. Increased abundance of *Veillonella*, *Klebsiella*, and *Selenomonas* species and lipopolysaccharide-producing bacteria but decreased abundance of *Bifidobacterium* species and butyrate-producing bacteria have been reported [99]. The association between *Helicobacter pylori*, a gastric pathogen that colonizes ~50% of individuals worldwide, and PDAC pathogenesis has been noted [100] but remains controversial.

The human tumor microbiome includes tumor type-specific intratumoral bacteria [101–103]. The α-diversity of the tumor microbiome was higher among individuals with increased long-term survival. An intratumoral microbiome signature (Pseudoxanthomonas-StreptomycesSaccharopolyspora-Bacillus clausilii) was
associated with long-term patient survival [102]. Altered gut microbiome composition and changes in host processing of bacteria-derived metabolites may imply the link between diabetes and PDAC initiation and progression with geographical, racial, dietary, and lifestyle-related differences [104].

KRAS-mutated cells prevail in competition under high-fat-induced inflammation

Not all pancreatic cells develop PanIN in genetically engineered mice with the Kras\textsuperscript{G12D} mutation, suggesting that additional factors are needed for the initial transformation. Figure 4
illuminates the current understanding of high glucose-triggered cancer initiation, which may be further promoted to become PDAC. Mutant cells are often recognized and passively eliminated from epithelial tissues through epithelial defense against cancer [105]. Kras-mutant cells drive metabolic reprogramming that enables them to rapidly grow and outcompete their adjacent regular counterparts to coexist with a large proportion of healthy cells in the preexisting general population [106]. High-fat diet feeding-induced inflammation promotes the coexistence of Kras-mutant cells with epithelia [107–109]. KrasG12D maintains an irreversible ADM through MAPK constitutive signaling to protect against inflammation-induced tissue damage [110]. The evidence provides certain clues for how Kras-mutated cancer cells may succeed in a nutrient competition.

**Functional genomics to uncover the metabolic dependence of PDAC**

Studies on the in vivo metabolic dependence of PDAC have been challenging due to the complexity and heterogeneity of the TME. Although there are limitations regarding intercellular nutrient sharing, in vivo metabolism-focused CRISPR screening in PDAC is expected to determine the essential global metabolic dependence for PDAC tumor growth [111, 112]. Current findings revealed that tumor growth depends on the crosstalk between the immune system and heme biosynthesis [111]. Genetic or pharmacological inhibition of farnesyl diphosphate farnesyl transferase delayed tumor growth and promoted CDB T-cell infiltration through PI3K/AKT signaling, indicating the potential targeting of cholesterol biosynthesis and autophagy to combat PDAC [112]. A new platform for characterizing metabolic dependencies under distinct genetic drivers or different PDAC statuses, such as initiation and metastasis, will provide a breakthrough for the field.

**BOX 1: COMPLEXITY OF GENETIC ALTERATIONS AND METABOLISM IN PDAC**

In addition to the most frequent oncogenic somatic mutation KRAS, a high percentage of patients carry inactivating somatic mutations in the tumor suppressors cyclin-dependent kinase inhibitor 2 A (CDKN2A), tumor protein 53 (TP53), and SMAD family member 4 (SMAD4) [113–115], reinforcing their roles during PanIN-to-PDAC [116]. Other mutations, such as those in Gα protein subunits (such as GNAS), MYC, TP53, and PTEN, drive metabolic shifts in PDAC. GNAS-activating mutations increase lipid utilization and fatty-acid oxidation to promote PDAC tumor progression [117]. MYC orchestrates metabolic reprogramming of PDAC progression through extrinsic and intrinsic factors via its natural role as a transcription factor [118–121]. TP53 controls cellular metabolism by directly modulating different transcriptional programs, such as the autophagy network [122], or redox control through the p53 target TIGAR [123, 124]. Restoration of wild-type p53 induces α-ketoglutarate accumulation to increase chromatin accessibility and tumor suppression [125]. Loss of the tumor suppressor PTEN hyperactivates phosphoinositide-3-kinase (PI3K)-AKT signaling and metabolic processes such as glucose metabolism, de novo lipid synthesis, and redox balance [126] and cooperates with mutant KRAS-driven events in multiple PDAC models [127–130].

There is still much room for metabolic efforts for early diagnosis and prevention. Approximately 3–10% of patients with PDAC carry inherited germline mutations in genes such as BRCA1 DNA repair-associated (BRCA1), BRCA2, and ATM serine/threonine kinase [131]. The direct functional link of BRCA1 and BRCA2 to the DNA damage response was first demonstrated [132, 133]. The discovery of more sensitive poly(ADP-ribose) polymerase (PARP) inhibition in BRCA-mutant cancer cells has led to the development of new biomarker-driven synthetic lethal treatment strategies for different cancers [134, 135]. However, in a mouse model of PDAC initiation, loss of heterozygosity (LOH) of BRCA2 while promoting chromosomal instability may not be essential for PDAC initiation [136]. Intriguingly, even in the presence of KRAS oncogenic mutations, BRCA2 LOH inhibits tumor formation when wild-type TP53 remains. BRCA2 LOH can accelerate PDAC tumorigenesis only after TP53 is mutated [137, 138]. PDAC metabolism shifts in response to the BRCAness phenotype remain to be elucidated. These findings postulated that the selected population sharing the BRCAness phenotype would be more sensitive to DNA damaging agents and DDR inhibitors. The appropriate subtype, therapeutic window, potential combination strategies, and functional differences of specific variants in the DDR pathway remain defined.

Approximately 5% of patients with PDAC carry RB mutations or deletions. RB was cloned and sequenced in the 1980s [139] and has been well characterized as a tumor suppressor for inhibiting the G0/G1 to S phase transition during cell cycle progression [140]. RB silences gene transcription by recruiting corepressor complexes, including histone deacetylases, to E2F transcription factors specifically targeting gene promoters [141]. Loss of RB inhibits glucose oxidation by directly inducing the expression of a glucose homeostasis sensor and modulator pyruvate dehydrogenase kinase 4 [141], promotes glutamine uptake via increased expression of the glutamine transporter and GLS1, perturbing redox homeostasis by reducing GSH levels [142]. However, the role and functional alteration of the loss of RB in PDAC development remain to be characterized.

**CONCLUDING REMARKS**

PDAC remains a difficult-to-treat cancer. Despite state-of-the-art comprehensive detection approaches, such as ultrasound, computed tomography scans, magnetic resonance imaging, and positron emission tomography scans, as well as treatment approaches such as surgery, radiation, chemotherapy, and immunotherapy, overall survival has not improved over the past several decades. Knowledge about metabolic dysregulation promoted by the Ras protein family, particularly mutant KRAS, has advanced substantially. Oncogenic KRAS mutations and their downstream reprogrammed metabolic pathways have been attractive therapeutic targets. Since metabolites such as glucose may trigger DNA damage and mutation through glucose metabolic reprogramming, a new niche for PDAC management has been emerged from these findings for early detection, prevention and treatment.

**DATA AVAILABILITY**

There are no experimental datasets given that this is a review article prepared based on the literature review. All the data supporting the findings of this review are available from the corresponding author upon reasonable request.

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YHL and WHL wrote the manuscript with input from all authors and were in charge of overall direction and planning. CMH and YSH assisted with literature analyses and comments. All authors discussed the results and provided critical feedback on the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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