

New Phenomenon

Glucose is a potential source of glutamate for glutamine-deprived pancreatic cancer cells with *KRAS* mutation

Zhiwen Xiao^{1,2,3,4,5,†}, Yiyi Li^{1,2,3,4,5,†}, Nuoyan Zhang^{6,†}, Yang Shi^{1,2,3,4,5}, Yilin Song^{1,2,3,4,5}, Yi Liu^{1,2,3,4,5}, Xinyue Wang^{1,2,3,4,5}, Quanxing Ni^{1,2,3,4,5}, and Guopei Luo^{1,2,3,4,5,*}

¹Department of Pancreatic Surgery, Fudan University Shanghai Cancer Center, Shanghai 200032, China, ²Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China, ³Shanghai Pancreatic Cancer Institute, Shanghai 200032, China, ⁴Shanghai Key Laboratory of Precision Medicine for Pancreatic Cancer, Shanghai 200032, China, ⁵Pancreatic Cancer Institute, Fudan University, Shanghai 200032, China, and ⁶Shanghai Key Laboratory of Plant Molecular Sciences, College of Life Sciences, Shanghai Normal University, Shanghai 200233, China

[†]These authors contributed equally to this work.

*Correspondence address. E-mail: luoguopei@fudanpci.org

Received 3 December 2025 Accepted 18 March 2026 Published 22 April 2026

Pancreatic cancer is a highly lethal malignancy, with a five-year survival of only 13% for pancreatic cancer overall and just 8% for the most common form, pancreatic adenocarcinoma [1]. Its aggressive nature is driven by key molecular events. Specifically, *KRAS* mutations, which occur in over 90% of cases, act as pivotal oncogenic driver [2]. Concurrently, profound metabolic reprogramming is a hallmark of pancreatic cancer. Research indicates that a glycolytic switch is activated very early, even in precancerous lesions. This switch is driven by factors such as the transcription factor SP1, which promotes tumorigenesis by activating glycolytic enzymes. This rewired glucose metabolism not only fuels tumor growth but also helps cancer cells evade novel cell death mechanisms such as copper-dependent cuproptosis [2–4].

Glutamate and glutamine play interconnected and important roles in pancreatic cancer metabolism, with their dysregulation driving tumor progression. Glutamine fuels carbohydrate antigen 19-9 (CA19-9) biosynthesis via the hexosamine pathway, and its blockade suppresses tumor growth and metastasis, suggesting a potential therapeutic strategy [5]. Building on the seminal 2013 study by Son *et al.* [6], which investigated the unique metabolic dependencies of pancreatic cancer, this research focused on glutamine's role. The study identified a critical, non-canonical glutamine metabolism pathway essential for pancreatic cancer tumor growth, regulated by the oncogenic *KRAS* mutation—a hallmark of this cancer. A major finding was that pancreatic cancer cells bypass the typical enzyme glutamate dehydrogenase (GLUD1) to channel glutamine into the tricarboxylic acid (TCA) cycle. Instead, they rely on a pathway where glutamine-derived aspartate is processed in the cytoplasm by aspartate transaminase (GOT1). Extracellular glutamine is the primary source for these cells. However, pancreatic tumors are often nutrient deficient. Under

glutamine deprivation, the cells may rewire glucose metabolism to generate glutamate, utilizing pathways involving α -ketoglutarate and non-canonical TCA cycle routes [7].

The relationship between glucose metabolism, diabetes, and pancreatic cancer is complex and bidirectional, involving both shared risk factors and direct metabolic consequences [8]. Long-standing type 2 diabetes is a well-established risk factor for pancreatic cancer, with diabetic patients having approximately twice the risk of developing pancreatic cancer compared to non-diabetic individuals. The high glucose environment of diabetes also upregulates the hexosamine biosynthetic pathway, increasing protein O-GlcNAcylation, which is linked to both insulin resistance and *KRAS* mutations in pancreatic cancer [9]. Conversely, pancreatic cancer itself can induce a unique form of diabetes known as pancreatic cancer-related diabetes mellitus (PDAC-DM) or type 3c diabetes [10]. This distinct entity arises when the malignant tumor disrupts the pancreas's endocrine function, leading to insulin deficiency and glucose intolerance. In the current study, patients diagnosed with pancreatic adenocarcinoma were selected from a prospectively (forward-looking) updated database within a single academic medical center (BioBank of Fudan University Shanghai Cancer Center) from 2021 to 2025. The criteria for case inclusion were as follows: (1) pathological confirmation of pancreatic adenocarcinoma from surgical specimen or biopsy; (2) adequate clinical information and follow-up data; and (3) information on baseline fasting blood glucose (FBG). Data recorded at the time of diagnosis, encompassing patient demographic information, previous diabetes history, FBG levels, and tumor biomarkers, were extracted. Baseline FBG measurements were taken under conditions where patients had abstained from calorie intake for a minimum of 8 h. Informed consent was obtained from the participants. The

study was approved by the Institutional Review Board (2008222-16). It is noteworthy that only 19.6% of patients had normal fasting glucose (684 cases; diabetes, 50.7%; impaired fasting glucose, 30.7%; Figure 1A). In addition, high fasting blood glucose (≥ 126 mg/dL) was confirmed to be an adverse prognostic factor for patients ($P = 0.028$; Figure 1B). In the multivariate Cox

regression model, elevated fasting blood glucose remained an adverse prognostic factor (hazard ratio, 1.41, 95% confidence interval, 1.07–1.86, $P = 0.015$) when adjusted for age, sex, tumor location, TNM stage, and pre-existing diabetes mellitus. These findings suggest that aberrant blood glucose plays a key role in pancreatic cancer progression.

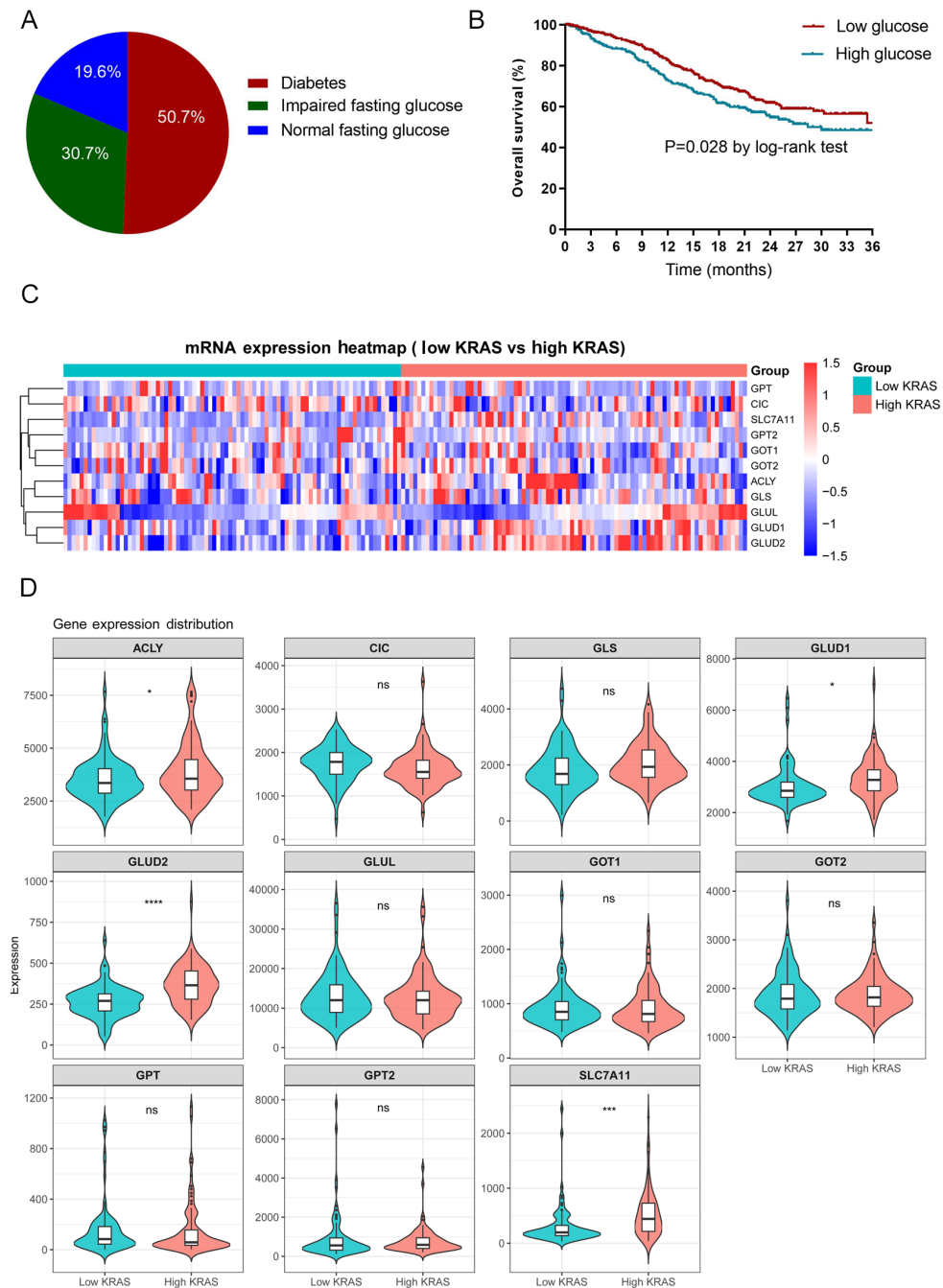


Figure 1. High glucose is associated with an adverse prognosis for patients with pancreatic cancer (A) Distribution of fasting blood glucose among pancreatic cancer patients (684 cases). Only 19.6% of patients with pancreatic cancer demonstrated fasting euglycemia. Normal fasting glucose, ≤ 99 mg/dL; Impaired fasting glucose, 100–125 mg/dL; Diabetes, ≥ 126 mg/dL. (B) Kaplan-Meier overall survival curve for patients with pancreatic cancer divided by baseline fasting blood glucose levels (hazard ratio = 1.34, 95% confidence interval, 1.03–1.74). Low glucose, < 126 mg/dL; high glucose, ≥ 126 mg/dL. (C) Heatmap illustrating mRNA expression levels of glutamate metabolism-related genes, including *GPT*, *GPT2*, *CIC*, *SLC7A11*, *GOT1*, *GOT2*, *ACLY*, *GLS*, *GLUL*, *GLUD1*, and *GLUD2*. (D) Violin plot and interquartile range depicting expression differences between low- and high-KRAS expression subgroups. *ACLY*, *GLUD1*, *GLUD2*, and *SLC7A11* exhibited significantly higher expression in the high-KRAS expression subgroup (Student's *t*-test, * $P < 0.05$, *** $P < 0.001$, **** $P < 0.0001$, and ns, $P > 0.05$).

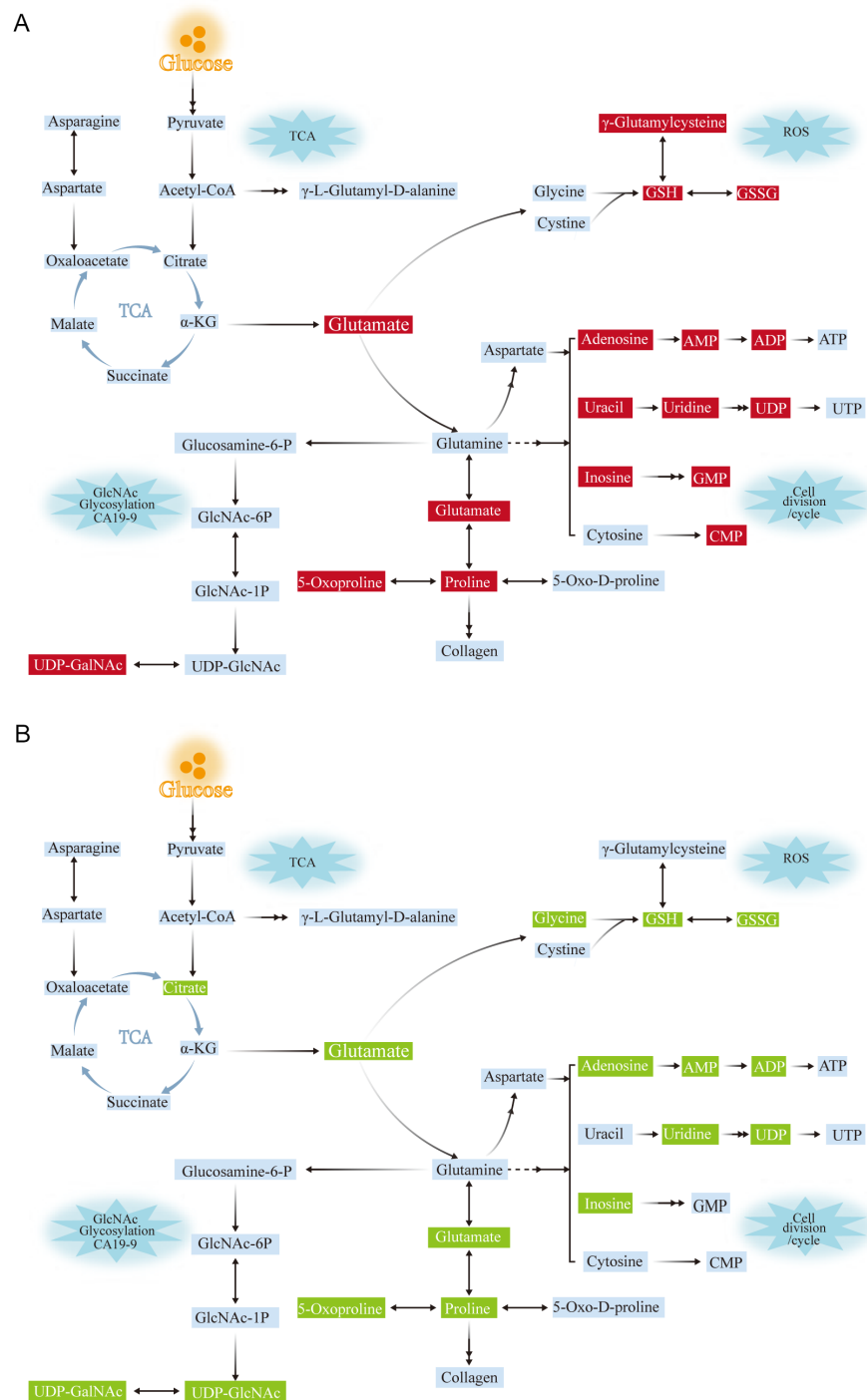


Figure 2. Glucose is reprogrammed to glutamate metabolism in pancreatic cancer cells (A) Metabolic flux of glucose in *KRAS*-mutated pancreatic cancer cells deprived of glutamine at different culture time points. After culture for 24 h, a main flow included glutamate and glutamate-related biological processes, including glycosylation (UDP-GlcNAc), collagen/stroma (proline, 5-oxoproline), cell division (adenosine, AMP, ADP, ATP, uracil, uridine, UDP, inosine, GMP, and CMP), and ROS reaction (GSH, GSSG, and γ -glutamylcysteine), detected by isotope tracing untargeted metabolomics using UHPLC-MS. (B) After culture for 48 h, in addition to the abovementioned metabolites, isotopes were also traced in UDP-GlcNAc, glycine, and citrate. Three replicates per condition. The double arrow represents multiple reactions using D-glucose- $^{13}\text{C}_6$ as a tracer. Red indicates metabolites that have been traced by isotope. UHPLC-MS, ultrahigh-performance liquid chromatography coupled with tandem Q Exactive Orbitrap mass spectrometer. α -KG, α -ketoglutarate; TCA cycle, tricarboxylic acid cycle; ROS, reactive oxygen species; CA19-9, sialyl Lewis a; UMP, uridine monophosphate; UDP, uridine 5'-diphosphate; UTP, uridine 5'-triphosphate; ADP, adenosine 5'-diphosphate; ATP, adenosine 5'-triphosphate; AMP, adenosine 5'-monophosphate; CMP, cytidine 5'-monophosphate; GMP, guanosine 5'-phosphate; GlcNAc-6P, N-acetylglucosamine-6-phosphate; GlcNAc-1P, N-acetylglucosamine-1-phosphate; UDP-GlcNAc, UDPN-acetylglucosamine.

The analysis utilized the TCGA Firehose Legacy cohort (http://www.cbioportal.org/study/summary?id=paad_tcga), which comprised 170 samples. *KRAS* mRNA expression levels were stratified using the median value as the cutoff. All continuous variables were analyzed using Student's *t* test or the Wilcoxon rank-sum test, as appropriate. The analysis of glutamate metabolism-related gene expression in pancreatic cancer patients stratified by *KRAS* expression levels revealed distinct patterns between low and high *KRAS* expression subgroups. As shown in the heatmap (Figure 1C), mRNA expression levels of key genes involved in glutamate metabolism—including *GPT*, *GPT2*, *CIC*, *SLC7A11*, *GOT1*, *GOT2*, *ALY*, *GLS*, *GLUL*, *GLUD1*, and *GLUD2*—were visualized, highlighting variability across samples. The violin plot further demonstrated significant expression differences between the two subgroups. Specifically, *ALY*, *GLUD1*, *GLUD2*, and *SLC7A11* were markedly upregulated in the high-*KRAS* expression group compared to the low-*KRAS* group (Figure 1D). These findings suggest that enhanced glutamate metabolism activity, particularly through these genes, may be associated with elevated *KRAS* expression in pancreatic cancer, potentially influencing tumor progression and metabolic reprogramming.

To trace the metabolic flux of glucose in *KRAS*-mutated pancreatic cancer cells using isotope tracing untargeted metabolomics, two pancreatic cancer cell lines with the *KRAS* G12V mutation [CFPAC1, CAPAN, from American Type Culture Collection (ATCC, Manassas, USA)] were cultured in medium deprived of glutamine, as previously described [5]. Cells were cultured for 24 h or 48 h in D-Glucose-¹³C₆ (4.5 g/L, 110187-42-3; Sigma-Aldrich, St Louis, USA). Cells cultured in unlabeled glucose (50-99-7; Sigma-Aldrich) were used as controls. A total of 1×10^7 cells were sent for analysis. Samples were prepared as previously described [5]. LC-MS/MS analyses were performed using a UHPLC system (1290; Agilent Technologies, Santa Clara, USA) with a UPLC HSS T3 column (2.1 mm $\times$ 100 mm, 1.8 μ m; Agilent Technologies) coupled to a Q Exactive mass spectrometer (Thermo Fisher Scientific, Waltham, USA). An in-house MS2 database (BiotreeDB, Shanghai, China) was applied for metabolite annotation (Supplementary Table S1). As shown in Figure 2A,B, glucose not only participates in established cellular processes such as the TCA cycle, cell division, and ROS response but also serves as a precursor for the synthesis of UDP-N-acetylglucosamine (UDP-GlcNAc) and UDP-N-acetyl-D-galactosamine (UDP-GalNAc), which are essential glycosylation substrates. Additionally, isotopic labeling was observed in proline and 5-oxo-D-proline, compounds structurally linked to collagen and extracellular matrix formation. All these metabolites are closely related to glutamate. Together, glucose is an important source of glutamate for glutamine-deprived pancreatic cancer cells with *KRAS* mutation, highlighting the dynamic role of glucose in sustaining critical cellular functions in *KRAS*-driven pancreatic cancer under glutamine limitation.

In summary, this study investigates the metabolic adaptations of pancreatic cancer cells with *KRAS* mutations under glutamine deprivation, revealing glucose as an alternative source of glutamate. Pancreatic cancer, driven by *KRAS* mutations in > 90% of cases, exhibits profound metabolic reprogramming, including early activation of glycolysis and reliance on non-canonical glutamine metabolism pathways. While extracellular glutamine is the primary

source, nutrient-deprived tumor cells rewire glucose metabolism to generate glutamate via α -ketoglutarate and alternative TCA cycle routes, bypassing the typical *GLUD1*-dependent pathway. Clinically, aberrant glucose metabolism is linked to poor outcomes: only 19.6% of patients had normal fasting glucose, and elevated fasting blood glucose (≥ 126 mg/dL) was independently associated with adverse prognosis. Using isotope tracing (D-glucose-¹³C₆) in *KRAS*-mutated cell lines (CFPAC1 and CAPAN), this study demonstrated that glucose-derived carbon flows into glutamate and related metabolites (e.g., proline, UDP-GalNAc) under glutamine deprivation, supporting tumor growth and metastasis. These findings highlight the therapeutic potential of targeting glucose-glutamine metabolic crosstalk in pancreatic cancer.

Supplementary Data

Supplementary data are available at *Acta Biochimica et Biophysica Sinica* online.

Data Availability

Data can be accessed upon reasonable request from the corresponding author.

Funding

This work was jointly supported by the grants from the National Natural Science Foundation of China (Nos. 81871940 and 82172625) and Shanghai Charity Foundation (No. HYXH2021042).

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Stoop TF, Javed AA, Oba A, Koerkamp BG, Seufferlein T, Wilmink JW, Besselink MG. Pancreatic cancer. *Lancet* 2025, 405: 1182–1202
2. Khan S, Budamagunta V, Zhou D. Targeting *KRAS* in pancreatic cancer: emerging therapeutic strategies. *Adv Cancer Res* 2023, 159: 145–184
3. Han HS, Hao MY, Li HJ, Li YG, Chu T, Wang YW, Si WR, *et al.* Role of disulfidptosis in cancer: molecular mechanisms and therapeutic opportunities. *Cell Signal* 2026, 141: 112277
4. Xu Y, Wu Y, Zheng X, Wang D, Ni H, Chen W, Wang K. A smart nanomedicine unleashes a dual assault of glucose starvation and cuproptosis to supercharge α PD-L1 therapy. *Adv Sci* 2025, 12: e2411378
5. Liu C, Deng S, Xiao Z, Lu R, Cheng H, Feng J, Shen X, *et al.* Glutamine is a substrate for glycosylation and CA19-9 biosynthesis through hexosamine biosynthetic pathway in pancreatic cancer. *Discov Oncol* 2023, 14: 20
6. Son J, Lyssiotis CA, Ying H, Wang X, Hua S, Ligorio M, Perera RM, *et al.* Glutamine supports pancreatic cancer growth through a *KRAS*-regulated metabolic pathway. *Nature* 2013, 496: 101–105
7. Arnold PK, Jackson BT, Paras KI, Brunner JS, Hart ML, Newsom OJ, Alibeckoff SP, *et al.* A non-canonical tricarboxylic acid cycle underlies cellular identity. *Nature* 2022, 603: 477–481
8. Chari ST. Diabetes and pancreatic cancer: a complex and confounding interplay. *Gut* 2025, 12: gutjnl-2025-336806
9. Zhu X, Xiao Z, Liu H, Zhang P, Deng S, Ding L, Feng J, *et al.* Pancreatic cancer: an exocrine tumor with endocrine characteristics. *Ann Surg* 2024, 280: e17–e25
10. Ng IK, Goh WG, Tho J, Teo DB. Sweet warning sign: new-onset diabetes mellitus as a Harbinger of pancreatic cancer. *Trop Doct* 2026, 56: 341–342