International Journal of Clinical Science and Medical Research

ISSN(print): 2770-5803, ISSN(online): 2770-582X

Volume 06 Issue 06 June 2026

DOI: https://doi.org/10.55677/IJCSMR/V6I6-08/2026, Impact Factor: 8.005

Page No : 193-205

Impact of High Sugar Intake on KRAS-Mediated Pancreatic Carcinogenesis in Diabetes Mellitus

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ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies worldwide, with a five-year survival rate below 12%, largely attributable to the absence of effective early detection strategies and the near-universal resistance to conventional systemic therapies. Activating mutations in the KRAS proto-oncogene—particularly $KRAS^{G12D}$ and $KRAS^{G12\beta}$—are detected in over 90% of PDAC cases and represent the earliest and most defining molecular events in pancreatic carcinogenesis. Concurrently, diabetes mellitus (DM) and high dietary sugar intake have emerged as significant risk factors for PDAC, with diabetic patients carrying approximately two to three times the risk of developing PDAC compared to non-diabetic individuals. Crucially, recent mechanistic evidence has established a direct molecular link between high-glucose environments and the preferential induction of de novo KRAS mutations in pancreatic cells. In high-glucose conditions, cellular O-linked N-acetylglucosamine (O-GlcNAc) modification is dramatically elevated due to upregulation of the hexosamine biosynthesis pathway (HBP). This O-GlcNAcylation specifically targets ribonucleotide reductase subunit 1 (RRM1/RNR), impairing its enzymatic activity, depleting deoxynucleotide triphosphate (dNTP) pools, and inducing genomic instability that preferentially generates $KRAS^{G12D}$ mutations in pancreatic cells. Once established, oncogenic KRAS drives comprehensive metabolic reprogramming including enhanced aerobic glycolysis (Warburg effect), activation of the HBP and pentose phosphate pathway (PPP), glutamine scavenging, and lipid biogenesis—all of which are further amplified by the hyperglycemic milieu of DM. Hyperinsulinemia, a hallmark of type 2 DM, independently accelerates pancreatic intraepithelial neoplasia (PanIN) progression through insulin receptor–mediated activation of PI3K/AKT and RAF/MEK/ERK cascades in acinar cells. High fructose intake, increasingly prevalent through consumption of high-fructose corn syrup and sucrose-rich diets, amplifies KRAS-MAPK signaling through ketohexokinase C (KHK-C) and mTORC1 co-activation. This review provides a comprehensive synthesis of the epidemiological, molecular, and preclinical evidence linking high sugar intake and DM to KRAS-mediated pancreatic carcinogenesis, examines the downstream oncogenic signaling networks, the consequent desmoplastic tumor microenvironment, and explores the translational implications for prevention and targeted therapy.

Published Online: June 11, 2026

KEYWORDS:

KRAS mutation; pancreatic ductal adenocarcinoma; diabetes mellitus; high sugar intake; O-GlcNAcylation; hexosamine biosynthesis; Warburg effect; hyperinsulinemia; PanIN; RAF/MEK/ERK; PI3K/AKT/mTOR

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Cite this Article: Asghar, M.S., Mubarak, M.H., Mubarak, M.H. (2026). Impact of High Sugar Intake on KRAS-Mediated Pancreatic Carcinogenesis in Diabetes Mellitus. International Journal of Clinical Science and Medical Research, 6(6), 193-205. https://doi.org/10.55677/IJCSMR/V6I6-08/2026

1. INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) represents the predominant histological subtype of pancreatic cancer, accounting for approximately 90–95% of all pancreatic malignancies. With an incidence of approximately 60,000 new cases per year in the United States alone and a five-year overall survival rate that has minimally improved to

approximately 11–12% despite decades of research, PDAC is projected to become the second leading cause of cancer-related death in the United States by approximately 2030 (Siegel et al., 2023). The dismal prognosis reflects a constellation of challenges: the absence of reliable early-detection biomarkers, the aggressive biological behavior of the disease, its propensity for early metastatic dissemination, the dense desmoplastic stroma that impedes drug delivery, and an immunosuppressive tumor microenvironment that renders conventional immunotherapy ineffective. Surgical resection, the only potentially curative intervention, is feasible in only 15–20% of patients at the time of diagnosis owing to the predominantly advanced stage at presentation.

The molecular hallmark of PDAC is activating point mutation in the KRAS proto-oncogene, which encodes a small GTPase serving as a master switch that transmits mitogenic signals from cell surface receptors to a plethora of downstream effector pathways. KRAS mutations are detected in over 90% of PDAC cases and represent the earliest identifiable genetic event in the multistep progression from normal ductal epithelium through pancreatic intraepithelial neoplasia (PanIN) grades 1–3 to invasive carcinoma (Waters & Der, 2018). The dominance of KRAS in PDAC pathogenesis—alongside co-occurring inactivation of CDKN2A, TP53, and SMAD4 has made it the most attractive therapeutic target in pancreatic oncology, albeit one whose clinical exploitation has been frustratingly limited until the very recent development of covalent inhibitors targeting $KRAS^{G12c}$ (Hallin et al., 2022).

Epidemiological and mechanistic evidence over the past two decades has firmly established diabetes mellitus (DM) and high dietary sugar intake as major modifiable risk factors for PDAC. Diabetic patients carry approximately two to three times the risk of developing PDAC compared to non-diabetic individuals, and at the time of diagnosis, nearly 80% of PDAC patients harbor either overt DM or impaired glucose tolerance (Sharma et al., 2022; Chari et al., 2008). This association is bidirectional and complex: long-standing DM predisposes to PDAC through chronic hyperglycemia, hyperinsulinemia, and inflammatory metabolic disruption, while PDAC itself frequently induces new-onset DM through destruction of pancreatic islet cells and secretion of adrenomodulin. High consumption of simple sugars—particularly free fructose from high-fructose corn syrup and sucrose-rich beverages—has been independently associated with elevated PDAC risk in prospective epidemiological cohorts. Mechanistically, landmark work by Hu et al. (2019) in Cell Metabolism demonstrated that high-glucose environments directly induce de novo $KRAS^{G12D}$ mutations in non-tumorigenic pancreatic cells through O-GlcNAcylation-mediated impairment of ribonucleotide reductase and consequent depletion of dNTP pools—providing the first direct biochemical mechanistic link between perturbed sugar metabolism and oncogenic KRAS mutagenesis.

This review synthesizes the current state of knowledge concerning the molecular interface between high sugar intake, diabetes mellitus, and KRAS-driven pancreatic carcinogenesis. We examine: (1) the molecular biology of KRAS in PDAC; (2) the epidemiology and pathophysiology of the DM–PDAC relationship; (3) the direct molecular mechanisms through which high glucose and fructose induce KRAS mutations; (4) KRAS-driven metabolic reprogramming and its amplification in the hyperglycemic milieu; (5) downstream oncogenic signaling pathways and their interactions with the diabetic metabolic environment; (6) the consequent tumor microenvironment; and (7) translational implications for chemoprevention, early detection, and molecularly targeted therapy.

2. KRAS IN PANCREATIC CANCER: MOLECULAR BIOLOGY AND MUTATIONAL LANDSCAPE

2.1 KRAS Structure and the GTPase Switch

KRAS encodes a 21 kDa GTPase that functions as a binary molecular switch, cycling between an active GTP-bound state and an inactive GDP-bound state. In its active conformation, KRAS recruits and activates effector proteins—most prominently RAF kinases, PI3K catalytic subunits, and RalGDS guanine nucleotide exchange factors—that relay mitogenic, survival, and metabolic signals to the nucleus. GTPase-activating proteins (GAPs), particularly NF1 (neurofibromin 1), catalyze the intrinsic GTP hydrolysis reaction by several orders of magnitude, returning KRAS to its inactive GDP-bound state (Waters & Der, 2018). The activating point mutations that characterize PDAC—predominantly at codons 12 and 13—abrogate the ability of GAPs to stimulate GTP hydrolysis, locking KRAS in a constitutively GTP-bound active state that sends continuous, unsuppressed mitogenic signals irrespective of extracellular growth factor cues.

The mutational spectrum of KRAS in PDAC is dominated by glycine-to-aspartate substitution at codon 12 (G12D, ~44%), followed by glycine-to-valine (G12V, ~34%) and glycine-to-arginine (G12R, ~20%) substitutions. The rare G12C substitution (~1.5–3%), exploited by the covalent inhibitors sotorasib and adagrasib that gained FDA approval for KRAS G12C-mutant non-small cell lung cancer in 2021–2022, is present in only a small minority of PDAC cases (Hallin et al., 2022). Each substitution confers subtly distinct biochemical properties—differing rates of intrinsic GTP hydrolysis, effector binding affinities, and downstream signaling strengths—that may explain in part the differences in clinical behavior among PDAC subtypes and their differential responsiveness to therapies. Critically, G12D—the most prevalent PDAC KRAS mutation—has been specifically shown to be induced preferentially by high-glucose-driven O-GlcNAcylation-mediated genomic instability in pancreatic cells (Hu et al., 2019), establishing a direct mutagenic link to the diabetic metabolic environment.

2.2 KRAS as the Initiating Oncogenic Driver in PDAC

Genetically engineered mouse models (GEMMs) have been invaluable in establishing the causal role of KRAS mutations in PDAC initiation and progression. The landmark KrasG12D mouse model, in which LSL-KrasG12D is conditionally activated in pancreatic cells through Pdx1-Cre or Ptf1a-Cre drivers, reliably develops PanIN lesions and, with longer latency, invasive PDAC, demonstrating that oncogenic KRAS is sufficient to initiate premalignant pancreatic lesions (Hingorani et al., 2003). Full progression to invasive PDAC in these models requires co-deletion of tumor suppressors Trp53, Cdkn2a (INK4a/ARF), or SMAD4, reflecting the multi-hit genetic progression of human PDAC. A central oncogenic function of KRAS in these models—and in human PDAC—is comprehensive metabolic reprogramming: KRAS G12D drives upregulation of glucose transporters (GLUT1, GLUT3), stimulates hexokinase II (HKII) and phosphofructokinase (PFK) to enhance glycolytic flux, directs glycolytic intermediates into the HBP and PPP for biosynthetic and redox purposes, and promotes glutamine scavenging to replenish TCA cycle intermediates in an EGFR-independent manner (Ying et al., 2012). These KRAS-directed metabolic adaptations are critically amplified when KRAS-mutant cells are exposed to the high-glucose and high-insulin environments characteristic of DM, creating a synergistic oncogenic context that accelerates PDAC progression (Sato et al., 2020).

Table 1. ***KRAS mutational subtypes in PDAC: frequencies, biochemical properties, and therapeutic targeting.***

KRAS Mutation	Frequency in PDAC	GTPase Activity	Sensitivity to Inhibitors	Key Reference
G12D	~44%	Severely impaired	MRTX1133 (preclinical); ASP3082 (Phase I)	Bournet et al., 2016
G12V	~34%	Severely impaired	No approved inhibitors; MEK/ERK targeting	Waters & Der, 2018
G12R	~20%	Partially retained	No approved inhibitors; PI3K pathway	Hobbs et al., 2020
G12C	~1.5–3%	Severely impaired	Sotorasib (FDA 2021); Adagrasib (FDA 2022)	Hallin et al., 2022
Q61H / Other	~4%	Severely impaired	Investigational; downstream inhibitors	Zeng et al., 2022

3. EPIDEMIOLOGY: HIGH SUGAR INTAKE, DIABETES MELLITUS, AND PDAC RISK

3.1 Diabetes Mellitus as a Risk Factor for PDAC

The epidemiological evidence linking diabetes mellitus to PDAC risk is extensive and consistent. A meta-analysis of 36 cohort studies encompassing over 9 million participants demonstrated that individuals with DM have a 1.8- to 2.1-fold increased risk of developing PDAC compared to non-diabetic controls (Ben et al., 2011). More recent analyses employing the UK Biobank cohort—comprising over 500,000 participants—have confirmed that diabetes is associated with more than a three-fold increased PDAC risk (Sharma et al., 2022). The temporal relationship between DM onset and PDAC diagnosis is particularly informative: long-standing type 2 DM (>5 years duration) is associated with an approximately 50% increased PDAC risk over background, and hyperglycemia has been independently identified as a risk factor for PDAC in patients with DM duration of five years or more (Sato et al., 2020). Conversely, new-onset DM within 12–24 months of PDAC diagnosis likely reflects DM as an early paraneoplastic manifestation of the developing tumor, mediated by adrenomodulin-dependent suppression of pancreatic β-cell insulin secretion and impaired insulin sensitivity from circulating tumor-derived factors.

The bidirectional nature of the DM–PDAC relationship complicates epidemiological interpretation: a subset of new-onset DM cases in older adults may represent a paraneoplastic marker of occult PDAC (pancreatogenic or type 3c DM), while long-standing DM represents a true predisposing condition. Large-scale screening studies suggest that approximately 0.85–1.5% of new-onset DM patients aged >50 years harbor occult PDAC at the time of DM diagnosis, providing a rationale for enriched surveillance strategies in this population. The metabolic disturbances of DM—chronic hyperglycemia, hyperinsulinemia, dyslipidemia, and elevated circulating IGF-1—together create a pro-carcinogenic pancreatic microenvironment that lowers the threshold for KRAS mutagenesis and enhances clonal expansion of KRAS-mutant cells (Aggarwal et al., 2013; Peters et al., 2021).

3.2 Dietary Sugar and Fructose as Independent PDAC Risk Factors

Independent of the DM–PDAC association, dietary sugar consumption—particularly high intake of fructose from sucrose and high-fructose corn syrup (HFCS)—has been identified as a PDAC risk factor in multiple prospective

epidemiological cohorts. Michaud et al. demonstrated that women with high glycemic load diets had significantly elevated PDAC risk compared to those with low glycemic load diets, particularly in the context of physical inactivity and overweight. Prospective cohort data consistently link daily consumption of sugar-sweetened beverages to a 70–87% elevated PDAC risk compared to non-consumers, independent of obesity and diabetes status (Mueller et al., 2010). A landmark study by Schernhammer et al. (2005) in the Health Professionals Follow-Up Study and Nurses' Health Study cohorts identified fructose—but not total carbohydrate intake—as an independent PDAC risk factor, suggesting that the specific metabolism of fructose, rather than generalized glycemic load, mediates the carcinogenic effect. Global fructose consumption has increased approximately five-fold between the 19th and 21st centuries, driven primarily by the widespread adoption of HFCS as a commercial sweetener, providing a plausible dietary explanation for rising PDAC incidence trends in industrialized nations.

4. DIRECT MECHANISMS: HIGH SUGAR-INDUCED KRAS MUTAGENESIS

4.1 Hexosamine Biosynthesis Pathway Upregulation and O-GlcNAcylation

The hexosamine biosynthesis pathway (HBP) represents a critical metabolic node that integrates glucose, glutamine, acetyl-CoA, and UTP into the final product UDP-N-acetylglucosamine (UDP-GlcNAc)—the obligate substrate for O-linked N-acetylglucosaminylation (O-GlcNAcylation) catalyzed by O-GlcNAc transferase (OGT). Under physiological glucose concentrations, approximately 2–5% of intracellular glucose flux is directed through the HBP. However, in high-glucose conditions—as encountered in the hyperglycemic pancreatic microenvironment of DM—the HBP flux increases dramatically, elevating intracellular UDP-GlcNAc levels and substantially increasing global O-GlcNAcylation of hundreds of nuclear, cytoplasmic, and mitochondrial proteins. In pancreatic cells specifically, this elevation in O-GlcNAcylation is amplified beyond what is observed in most other cell types due to their characteristically low phosphofructokinase (PFK) activity: unlike cells with high PFK activity that efficiently commit glucose to glycolysis, pancreatic cells with low PFK activity accumulate fructose-6-phosphate upstream of PFK, which is preferentially shunted into the HBP, creating a cell-type-specific vulnerability to HBP-mediated genomic instability (Hu et al., 2019).

The critical oncogenic consequence of O-GlcNAcylation in pancreatic cells under high-glucose conditions is the modification of ribonucleotide reductase subunit M1 (RRM1) at threonine 734 (T734). RRM1, which forms the large subunit of ribonucleotide reductase (RNR), is the rate-limiting enzyme for conversion of ribonucleoside diphosphates to deoxyribonucleoside diphosphates (dNDPs) and is essential for maintaining balanced dNTP pools necessary for accurate DNA replication and repair. O-GlcNAcylation of RRM1 at T734 alters its binding affinity to the small subunit RRM2, reducing overall RNR catalytic activity and creating a deficiency in the cellular dNTP pool. This dNTP imbalance increases DNA polymerase error rate, particularly at guanosine residues in the KRAS codon 12, preferentially inducing the GGT-to-GAT single-nucleotide variant that encodes the glycine-to-aspartate (G12D) substitution—precisely the most prevalent KRAS mutation in PDAC. Landmark experiments by Hu et al. (2019) demonstrated that high-glucose treatment of non-tumorigenic human pancreatic ductal epithelial cells dose-dependently increased KRAS G12D somatic mutation frequency, and that this effect was significantly attenuated by pharmacological inhibition of OGT, establishing direct causality in the high glucose → HBP → O-GlcNAc-RRM1 → dNTP depletion → $KRAS^{G12D}$ mutation pathway.

4.2 STAT3 Phosphorylation and PanIN Progression Under Hyperglycemia

Beyond direct mutagenesis, hyperglycemia accelerates the progression of established PanIN lesions in KRAS-mutant pancreatic cells through non-mutagenic proliferative and survival signaling. Sato et al. (2020) demonstrated in $Kras^{gtgG12D}$ mice subjected to streptozotocin-induced hyperglycemia that hyperglycemia significantly accelerated PanIN formation and progression compared to euglycemic KRAS-mutant controls. In vitro, high-glucose medium (25 mM) increased cell viability and sphere formation in KRAS-mutant human PDAC lines (PANC-1, BxPC-3 cells with KRAS mutations) but not in KRAS-wild-type cells, confirming that the promoting effect of hyperglycemia is specifically dependent on oncogenic KRAS. Mechanistically, hyperglycemia strengthened STAT3 phosphorylation at tyrosine 705 (pSTAT3-Y705) and elevated MYC protein expression in a KRAS-dependent manner, suggesting that the synergy between high glucose and KRAS mutation operates through JAK-STAT3–MYC transcriptional amplification of metabolic reprogramming. Immunohistochemistry in pancreata from diabetic KRAS-mutant mice confirmed stronger pSTAT3 and MYC staining in PanIN lesions compared to euglycemic counterparts, establishing in vivo relevance.

4.3 Fructose-Specific Mechanisms: KHK-C and KRAS-MAPK Amplification

Dietary fructose exerts PDAC-promoting effects through mechanisms partially distinct from those of glucose, centered on ketohexokinase C (KHK-C), the rate-limiting enzyme of fructose metabolism. Unlike glucose, which feeds into glycolysis through hexokinase-dependent phosphorylation regulated by feedback inhibition, fructose is phosphorylated by KHK-C to fructose-1-phosphate in an essentially unregulated fashion, creating a substrate for glycolytic and biosynthetic pathways that bypasses the principal regulatory

steps of glucose metabolism. Zhang et al. (2017) demonstrated that dietary fructose promoted the development of aggressive PDAC in mice conditionally expressing $KRAS^{G12D}$ in the adult pancreas. Genetic inactivation of KHK-C improved survival in KPC (KrasG12D/+; Trp53R172H/+) mice, decreased viability and migratory capability of KPC cells, and—critically—strongly impaired activation of the KRAS-MAPK pathway and mTORC1 signaling, suggesting that fructose amplifies the oncogenic output of KRAS G12D through KHK-C–dependent augmentation of MAPK and mTOR signaling. Furthermore, high fructose intake promotes changes in glycoprotein sialylation—specifically elevating β-galactoside α2,6-sialyltransferase 1 (ST6Gal1) expression in a fructose-responsive manner—which enhances integrin-mediated invasion and metastatic potential of PDAC cells (Zhang et al., 2017).

The mTORC1 pathway represents a key convergence point for glucose- and fructose-mediated PDAC promotion: elevated glucose activates mTORC1 through PI3K-AKT-TSC1/2 axis; fructose catabolism generates metabolites that activate mTORC1 independently through nutrient sensing mechanisms; and oncogenic KRAS constitutively activates PI3K, creating a three-way convergent stimulation of mTORC1 that maximizes anabolic metabolism, protein synthesis, and proliferative capacity in the hyperglycemic, high-fructose context of contemporary Western dietary patterns (Noe et al., 2024).

Table 2. ***Molecular mechanisms through which high sugar intake induces KRAS mutagenesis and promotes PanIN progression in the diabetic pancreatic microenvironment.***

Mechanism	Key Molecular Players	Oncogenic Consequence	Reference
Hexosamine Biosynthesis Pathway (HBP) upregulation	GFAT, OGT, PFK-O-GlcNAcylation	Redirects glucose to O-GlcNAc modification	Hu et al., 2019
O-GlcNAcylation of RRM1 (ribonucleotide reductase)	RNR/RRM1-T734, OGT	Reduces dNTP pools; genome instability; KRAS G12D de novo mutation	Hu et al., 2019
Phosphofructokinase (PFK) O-GlcNAcylation	PFK-L, OGT, HBP feedback	Impairs glycolysis; HBP amplification loop	Hu et al., 2019
Hyperinsulinemia / IGF-1 axis	Insulin receptor, IGF-1R, PI3K, MAPK	PanIN initiation; acinar-to-ductal metaplasia	Chung et al., 2020
STAT3 phosphorylation by hyperglycemia	pSTAT3, MYC, GLUT1	Enhanced PanIN progression in Kras-mutant cells	Sato et al., 2020
Fructose via KHK and KRAS-MAPK	KHK-C, KRAS, rpS6, mTORC1	Promotes PDAC growth and metastasis; sialylation changes	Zhang et al., 2017
Advanced Glycation End-products (AGEs)	RAGE, NF-κB, ROS, IL-6, TNF-α	Chronic inflammation; KRAS co-activation	Deng et al., 2019

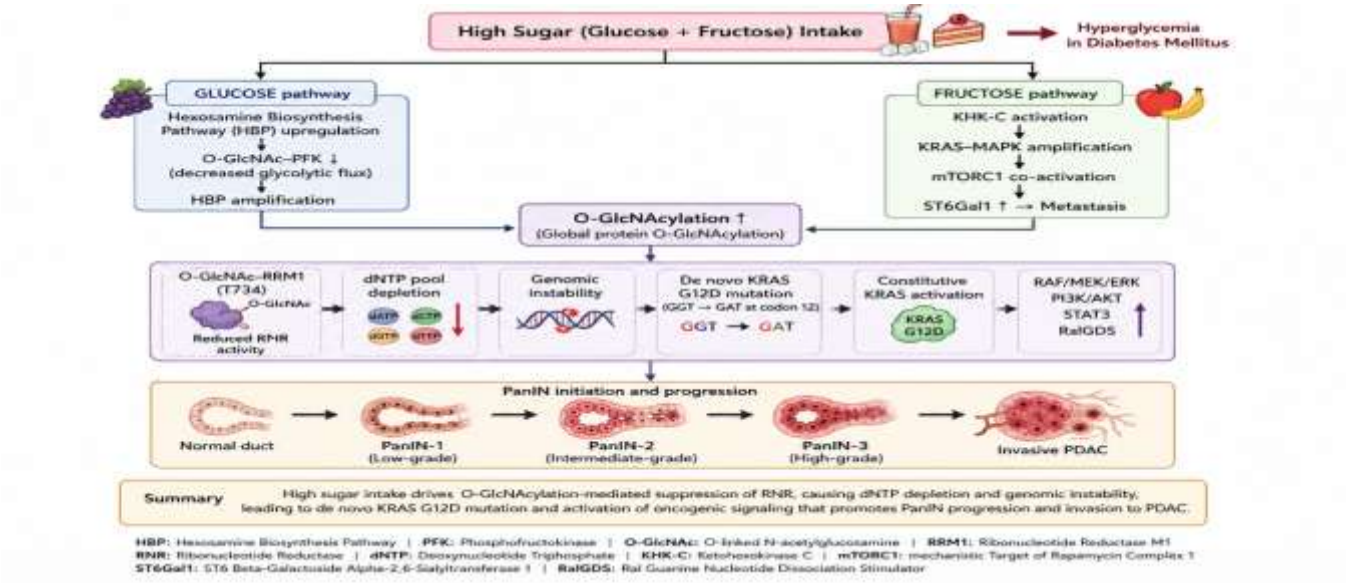

Figure 01 — ***Mechanistic pathway from high sugar intake through O-GlcNAcylation-mediated dNTP depletion to de novo KRAS G12D mutagenesis and subsequent PanIN-to-PDAC progression.***

5. KRAS-DRIVEN METABOLIC REPROGRAMMING AND AMPLIFICATION BY HYPERGLYCEMIA

5.1 The Warburg Effect and Glycolytic Upregulation

A canonical oncogenic function of KRAS G12D is the enforcement of aerobic glycolysis—the Warburg effect—wherein cancer cells preferentially metabolize glucose through glycolysis and lactate fermentation even in the presence of adequate oxygen, rather than completing glucose oxidation through oxidative phosphorylation. KRAS G12D drives this metabolic switch by upregulating glucose transporters (GLUT1, GLUT3) through RAF/MEK/ERK-mediated transcriptional activation of HIF-1α and MYC, enhancing hexokinase II (HKII) expression to commit glucose to glycolysis, upregulating phosphofructokinase and pyruvate kinase M2 (PKM2), and inducing lactate dehydrogenase A (LDHA) to regenerate NAD+ and maintain glycolytic flux (Ying et al., 2012; Guerra et al., 2011). The net result is a dramatic increase in glucose uptake and lactate secretion that provides rapid ATP generation and—more importantly—channels glycolytic intermediates into anabolic biosynthetic pathways.

In the diabetic hyperglycemic context, the KRAS-upregulated glucose transporters encounter elevated extracellular glucose concentrations, markedly amplifying intracellular glucose flux and glycolytic output. The resulting excess of glycolytic intermediates (glucose-6-phosphate, fructose-6-phosphate) further feeds the HBP and PPP at rates that exceed what KRAS activation alone would achieve. This creates a positive feedback loop: KRAS-upregulated GLUT1 in the hyperglycemic DM environment increases glucose uptake → elevated fructose-6-phosphate → HBP upregulation → O-GlcNAc modification of further KRAS pathway effectors (including KRAS itself via KRAS O-GlcNAcylation which reduces GAP sensitivity) → augmented KRAS oncogenic signaling → further GLUT1 upregulation (Zhu et al., 2020).

5.2 Hexosamine Biosynthesis and Pentose Phosphate Pathways

The HBP and PPP represent two critical biosynthetic branches of glucose metabolism that are coordinately upregulated by KRAS G12D and amplified under hyperglycemic conditions. In the HBP, glucose is converted through GFAT (glutamine:fructose-6-phosphate amidotransferase)—the rate-limiting enzyme—to ultimately produce UDP-GlcNAc, which serves as the substrate for protein O-GlcNAcylation and N-glycosylation. KRAS G12D has been shown to upregulate GFAT expression through NFkB and MYC transcriptional programs, augmenting HBP flux and contributing to the hyperglycosylation of signaling proteins including RAS effectors and transcription factors that sustain the oncogenic phenotype. O-GlcNAcylation of oncogenic transcription factor SOX2 in pancreatic cancer cells has been shown to promote tumor initiation, linking HBP-mediated protein modification directly to transcriptional reprogramming (Sharma et al., 2018).

In the PPP, KRAS G12D upregulates glucose-6-phosphate dehydrogenase (G6PD) and 6-phosphogluconate dehydrogenase (6PGD) to divert glucose-6-phosphate into ribose-5-phosphate synthesis (for nucleotide biogenesis) and NADPH production (for anabolic reductions and ROS detoxification). The increased PPP flux under KRAS G12D is further stimulated in the hyperglycemic context by the elevated glucose-6-phosphate supply and by NRF2-mediated transcriptional upregulation of G6PD—NRF2 being a direct transcriptional target of KRAS oncogenic signaling (Di Giorgio et al., 2023). The NADPH produced by the PPP is critical for glutathione regeneration and thus for neutralizing the elevated reactive oxygen species (ROS) generated by the metabolically hyperactive KRAS-mutant pancreatic cancer cell, providing a survival advantage in the oxidatively stressful tumor microenvironment.

6. DOWNSTREAM ONCOGENIC SIGNALING PATHWAYS

6.1 RAF/MEK/ERK Pathway

The RAF/MEK/ERK cascade is the principal effector pathway activated by oncogenic KRAS in PDAC and constitutes the most extensively studied pro-tumorigenic signal transduction axis in this malignancy. Constitutively GTP-bound KRAS G12D directly binds to and activates RAF kinases (BRAF and CRAF), which phosphorylate and activate the dual-specificity kinases MEK1 and MEK2, which in turn phosphorylate and activate ERK1/2. Activated ERK1/2 translocates to the nucleus to phosphorylate and activate transcription factors including ELK1, c-FOS, and c-MYC, driving the expression of cyclins, CDKs, and metabolic genes that collectively promote cell cycle entry, proliferation, and metabolic reprogramming (Zeitouni et al., 2016). In the context of DM, the RAF/MEK/ERK pathway is co-activated by hyperinsulinemia-mediated insulin receptor (INSR) signaling, which recruits IRS1/2 adaptors that activate RAS through SOS1/2 guanine nucleotide exchange factors, creating a synergistic amplification of ERK activation in KRAS-mutant pancreatic cells (Peters et al., 2021). Elevated circulating IGF-1—a consequence of DM-associated hyperinsulinemia-driven hepatic IGF-1 release—further amplifies this axis by engaging IGF-1R, which cross-activates RAS signaling and synergizes with KRAS G12D to sustain constitutive ERK activation beyond what either stimulus alone would achieve.

6.2 PI3K/AKT/mTOR Pathway

The PI3K/AKT/mTOR pathway is the second major effector pathway activated by KRAS G12D and is equally important in DM-associated PDAC pathobiology. KRAS G12D directly binds and activates PI3Kα (PIK3CA), elevating PIP3 production and activating PDK1-mediated AKT phosphorylation at Thr308 and mTORC2-mediated AKT

phosphorylation at Ser473. Activated AKT promotes cell survival through phosphorylation of BAD, MDM2 (suppressing p53), and FOXO transcription factors (excluding them from the nucleus), and activates mTORC1 through phosphorylation of TSC1/2–RHEB axis, promoting cap-dependent translation, lipid biosynthesis, and suppression of autophagy (Zeitouni et al., 2016). In the diabetic context, hyperinsulinemia provides a strong co-activating signal through INSR-IRS1-PI3K signaling that converges with KRAS G12D-driven PI3K activation, creating compounded mTORC1 hyperactivation that maximally stimulates protein synthesis and anabolic metabolism. Crucially, insulin receptor-mediated PI3K-AKT-mTOR activation in acinar cells expressing KRAS G12D was shown to be specifically required for hyperinsulinemia-driven PanIN initiation and acinar-to-ductal metaplasia (Chung et al., 2020), establishing insulin receptor signaling in acinar cells as a mechanistic link between DM and KRAS-dependent pancreatic carcinogenesis.

6.3 STAT3, NF-κB, and Inflammatory Signaling

Oncogenic KRAS G12D promotes inflammatory signaling through multiple mechanisms including NF-κB pathway activation (through RALGDS-mediated TIAM1 and RAC1 engagement) and autocrine cytokine signaling that activates JAK-STAT3 pathways. KRAS G12D induces expression of IL-6, IL-8, IL-1β, CXCL1, and granulocyte-colony stimulating factor (G-CSF), which recruit immunosuppressive myeloid cells and cancer-associated fibroblasts (CAFs) to establish the desmoplastic tumor microenvironment. The advanced glycation end-products (AGEs) generated by chronic hyperglycemia in DM engage the receptor for AGE (RAGE) on pancreatic cells and stromal components, activating NF-κB and STAT3 signaling that synergizes with KRAS-driven inflammatory programs to create an amplified inflammatory microenvironment conducive to PanIN progression and malignant transformation (Deng et al., 2019). In Kras G12D mice, hyperglycemia-induced pSTAT3 elevation in PanIN cells directly enhanced MYC expression and accelerated progression through higher-grade PanIN lesions to invasive PDAC, an effect that was attenuated by JAK inhibitor treatment, establishing STAT3 as a therapeutic target at the DM–KRAS interface (Sato et al., 2020).

Table 3. ***KRAS-activated downstream signaling pathways, their metabolic and oncogenic effects, and therapeutic targeting strategies in PDAC.***

Signaling Pathway	Key Components	Metabolic / Oncogenic Effect	Therapeutic Target
RAF/MEK/ERK	BRAF, CRAF, MEK1/2, ERK1/2	Upregulates GLUT1, HK2, LDHA; drives Warburg glycolysis; proliferation	MEK inhibitors (trametinib, cobimetinib) - clinical trials
PI3K/AKT/mTOR	PI3Kα, AKT1/2, mTORC1/2	Stimulates HBP flux, protein synthesis, survival; glucose transporter upregulation	Alpelisib, everolimus; combination with MEK inhibitors
STAT3	JAK2, STAT3, MYC	PanIN progression under hyperglycemia; immune evasion; PD-L1 upregulation	Ruxolitinib, napabucasin; combination strategies
NRF2/KEAP1	NRF2, KEAP1, p62, HO-1	ROS detoxification; redirects PPP for NADPH; promotes survival under oxidative stress	Investigational NRF2 inhibitors (brusatol, ML385)
NF-κB / Inflammatory	IKKβ, NF-κB, IL-6, TNF-α, COX-2	Stromal desmoplasia; macrophage polarization; AGE-RAGE axis activation	Anti-inflammatory (celecoxib); JAK/STAT inhibitors
RalGDS / RAL	RalA, RalB, TBK1, NF-κB	Autophagy regulation; mitochondrial fission; metastatic signaling	TBK1 inhibitors; RAL-GEF inhibitors (investigational)

7. TUMOR MICROENVIRONMENT AND DESMOPLASTIC STROMA IN DM-ASSOCIATED PDAC

The PDAC tumor microenvironment (TME) is characterized by a dense desmoplastic stroma that can constitute up to 90% of the total tumor volume, creating extraordinarily high interstitial fluid pressure, collapse of the tumor vasculature, profound nutrient and oxygen deprivation, and a near-impenetrable physical barrier to drug delivery and cytotoxic immune cell infiltration. The desmoplastic stroma is

orchestrated primarily by cancer-associated fibroblasts (CAFs) and pancreatic stellate cells (PSCs), which are activated by KRAS-derived growth factors (TGF-β, PDGF, sonic hedgehog) and deposit collagen I, fibronectin, and hyaluronan into the extracellular matrix. Immunologically, the PDAC TME is profoundly immunosuppressive, enriched in M2-polarized tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs), while CD8+ effector T cells are effectively excluded by stromal barriers and checkpoint ligands (PD-L1, CTLA-4) expressed by tumor cells and macrophages (Wang et al., 2020).

The diabetic metabolic environment specifically modulates the PDAC TME in ways that may further entrench its immunosuppressive character. Hyperglycemia promotes M2 macrophage polarization through AGE-RAGE-NF-κB signaling, reducing M1 anti-tumor macrophage activity. Hyperinsulinemia drives enhanced fibrotic stromal deposition by activating IGF-1R signaling on PSCs, amplifying desmoplasia beyond what KRAS-derived signals alone would induce. Elevated circulating TGF-β in T2DM patients reinforces SMAD4-mediated fibrotic programs in CAFs, contributing to the dense collagenous matrix. Conversely, KRAS G12D treatment with the recently developed G12D-selective inhibitor MRTX1133 induced marked TME remodeling—including increased vascular density, M1 macrophage repolarization, reduced MDSC infiltration, and increased CD8+ T cell influx—suggesting that direct KRAS targeting can partially reverse the immunosuppressive TME and may restore immunotherapy sensitivity (Hallin et al., 2022).

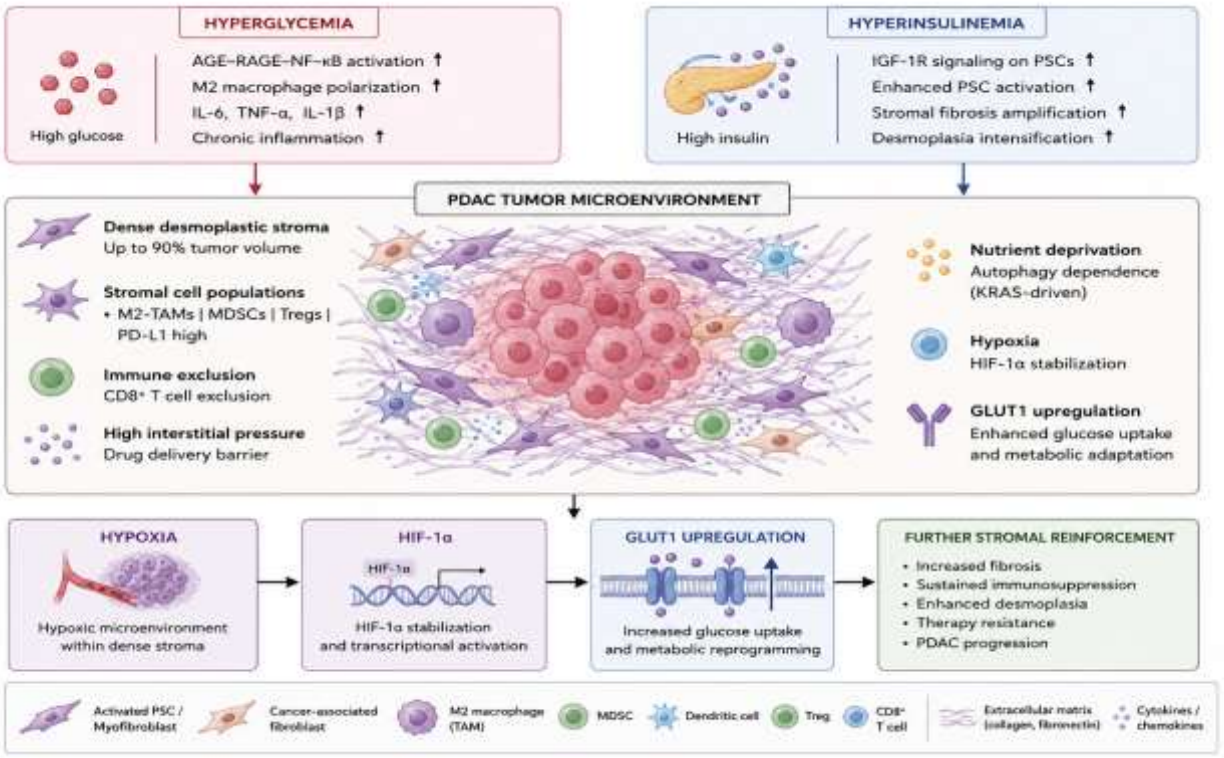

Figure 02 — ***Impact of the diabetic metabolic environment on the PDAC desmoplastic tumor microenvironment, showing reinforcement of immunosuppressive and fibrotic stromal programs.***

8. HYPERINSULINEMIA, IGF-1 AXIS, AND PDAC INITIATION

Hyperinsulinemia, which precedes hyperglycemia in the pathogenesis of type 2 DM and is a defining feature of insulin-resistant obesity, exerts independent and mechanistically distinct pro-carcinogenic effects in KRAS-driven pancreatic carcinogenesis. The pancreatic acinar cell is extraordinarily well-supplied with insulin through intrapancreatic portal circulation, exposing it to supraphysiological insulin concentrations that substantially exceed those in peripheral circulation. Chung et al. (2020) provided the definitive experimental evidence that hyperinsulinemia drives PanIN initiation through a direct, cell-autonomous mechanism: insulin receptors (INSR) on KrasG12D-expressing acinar cells are dispensable for glucose homeostasis but specifically required for hyperinsulinemia-induced PanIN formation in the context of diet-induced obesity. INSR signaling in acinar cells enhanced digestive enzyme production and acinar inflammation, creating a state of chronic acinar stress that facilitates acinar-to-ductal metaplasia (ADM)—the critical cellular reprogramming step that converts acinar cells to a ductal-like progenitor state from which PanIN lesions arise. Genetic deletion of acinar INSR specifically abolished PanIN formation in hyperinsulinemic KRAS-mutant mice without affecting peripheral glucose metabolism, establishing a pancreas-specific insulin-KRAS carcinogenic axis.

Hyperinsulinemia additionally drives increased hepatic production and reduced IGFBP-1/3 expression, elevating circulating free IGF-1 concentrations. IGF-1 and IGF-2 bind IGF-1R, which is highly expressed on pancreatic ductal cells, and activate PI3K-AKT and MAPK pathways that are structurally identical to those activated by KRAS G12D, thereby co-amplifying the oncogenic signal transduction landscape of KRAS-mutant pancreatic cells (Peters et al., 2021). IGF-1R and INSR can also form hybrid receptors with intermediate binding affinities for insulin and IGF-1, creating a promiscuous growth factor receptor landscape in the hyperinsulinemic DM context that maximizes pro-proliferative signaling in KRAS-mutant cells. The convergent activation of PI3K-AKT and MAPK through INSR/IGF-1R and KRAS G12D creates a synergistic proliferative advantage that explains, at least in part, why the combination of DM and KRAS mutation creates a particularly aggressive oncogenic context.

9. CLINICAL SIGNIFICANCE: DIAGNOSIS, PREVENTION, AND THERAPEUTIC STRATEGIES

9.1 Early Detection in High-Risk Diabetic Populations

The epidemiological and mechanistic evidence reviewed herein has significant implications for early detection of PDAC in the diabetic population. Given that approximately 0.85–1.5% of new-onset DM patients over age 50 harbor occult PDAC, and that the DM–PDAC relationship is now mechanistically grounded in KRAS mutagenesis through hyperglycemia, there is a compelling case for enriched PDAC surveillance in carefully defined high-risk diabetic subgroups. Biomarker strategies currently under investigation in this context include: serum CA19-9 combined with plasma ctDNA detection of KRAS mutations; urinary O-GlcNAc modification profiles as surrogate markers of HBP activation; and novel biomarker panels incorporating adrenomodulin, IGFBP-2, and OGlcNAcylated RRM1 peptides. Endoscopic ultrasound (EUS) with fine needle aspiration remains the gold standard for tissue diagnosis in patients with suspicious pancreatic lesions identified on cross-sectional imaging, and its integration into surveillance protocols for high-risk diabetic patients with elevated CA19-9 is supported by cost-effectiveness modeling. Artificial intelligence-assisted analysis of electronic health records—integrating new-onset DM, weight loss, abdominal pain, and glycemic trajectory data—is emerging as a powerful tool for identifying PDAC among the vast diabetic population (Kenner et al., 2021).

9.2 Metformin as a Chemopreventive Strategy

Metformin, the most widely prescribed antidiabetic agent, has attracted significant interest as a PDAC chemopreventive agent, particularly in the DM context where its utility for glucose management coincides with mechanistic actions relevant to KRAS-driven carcinogenesis. Metformin inhibits mitochondrial complex I, activating AMPK, which phosphorylates and activates TSC2 to suppress mTORC1 and simultaneously reduces hepatic glucose output to lower circulating glucose and insulin levels. In KrasG12D mouse models subjected to high-fat, high-calorie diet (HFCD) to induce obesity-associated hyperinsulinemia, metformin prevented HFCD-induced weight gain, hepatic steatosis, and stimulation of ERK and mTORC1 in the pancreas, and significantly reduced the formation of advanced PanIN lesions compared to HFCD-fed controls without metformin (Collisson et al., 2012). Population-based studies have shown that metformin use in diabetic patients is associated with a 20–62% reduction in PDAC risk compared to diabetics not using metformin, though the magnitude of this benefit has been subject to debate due to potential methodological confounding. Mechanistically, metformin's AMPK-mediated inhibition of HBP flux—by reducing the GFAT substrate supply through lower glucose availability—could potentially attenuate the O-GlcNAcylation-driven KRAS mutagenesis pathway, providing a direct mechanistic rationale for its chemopreventive potential.

9.3 Targeting Oncogenic KRAS: Progress and Challenges

The historically 'undruggable' reputation of RAS proteins has been fundamentally challenged over the past decade by the development of covalent small molecules that exploit the cysteine residue introduced by the G12C substitution. Sotorasib (AMG 510) and adagrasib (MRTX849) covalently and irreversibly bind to KRAS G12C in the GDP-bound inactive state, preventing GEF-mediated nucleotide exchange and maintaining KRAS in an inactive conformation. These agents received FDA accelerated approval for KRAS G12C-mutant NSCLC in 2021 and 2022, respectively, but the G12C mutation occurs in only approximately 1–3% of PDAC cases (Hallin et al., 2022), severely limiting their applicability. For the far more prevalent G12D mutation that constitutes approximately 44% of PDAC cases and is specifically linked to high-glucose-induced mutagenesis, MRTX1133—a highly selective non-covalent KRAS G12D inhibitor—has demonstrated potent preclinical efficacy in PDAC cell lines and GEMMs, inducing not only direct anti-tumor effects but also significant TME remodeling with increased anti-tumor immune infiltration. Phase I clinical evaluation of MRTX1133 is ongoing. ASP3082, a KRAS G12D-selective proteolysis-targeting chimera (PROTAC) that catalytically degrades KRAS G12D protein via the ubiquitin-proteasome system, represents an alternative approach currently in Phase I trials (Drake et al., 2022).

Downstream pathway inhibition through MEK inhibitors (trametinib, cobimetinib) has shown preclinical promise, particularly in combination with metabolic targeting of the Warburg effect. Glucose metabolism sensitization—using glucose transporter inhibitors (BAY-876, WZB117) or glycolytic enzyme inhibitors (2-deoxyglucose, 3PO)—synergizes with MEK inhibition in KRAS-mutant PDAC models by simultaneously removing the metabolic fuel supply that KRAS G12D depends on and blocking the oncogenic signaling that sustains metabolic reprogramming.

The combination of MEK inhibition with autophagy inhibitors (hydroxychloroquine)—exploiting the dependency of KRAS-mutant cells on autophagy for survival under MEK inhibitor-induced metabolic stress—is currently being evaluated in Phase I/II clinical trials and represents a mechanistically rational strategy for KRAS-addicted PDAC (White et al., 2021).

Table 4. ***Clinical trials and emerging therapeutic strategies targeting the high sugar–KRAS–PDAC pathway.***

Agent / Strategy	Target	Context	Phase	Key Finding / Status
Gemcitabine + nab-paclitaxel	Nucleoside analog + tubulin	All-comers PDAC (1L)	Approved	OS 8.5 mo; standard of care in advanced PDAC
FOLFIRINOX	Cytotoxic combination	ECOG PS 0-1 PDAC (1L)	Approved	OS 11.1 mo; superior to gemcitabine alone
Sotorasib (AMG 510)	KRAS G12C	KRAS G12C-mutant PDAC	Phase I/II	~21% response; limited by rare G12C freq. in PDAC
MRTX1133	KRAS G12D	KRAS G12D PDAC (most common)	Phase I (ongoing)	Promising preclinical data; TME remodeling observed
ASP3082 (PROTAC)	KRAS G12D degrader	KRAS G12D PDAC	Phase I	First PROTAC in clinical evaluation for PDAC
Metformin (chemoprevention)	AMPK activation / mTOR suppression	T2DM + high PDAC risk	Observational / Phase II	Reduced PDAC incidence in diabetic cohorts; preclinical benefit in KrasG12D mice
MEK inhibitor (trametinib) + PARP inhibitor	MEK1/2 + PARP1/2	KRAS-mutant PDAC + HRD	Phase II	Synthetic lethality in KRAS-mutant + BRCA-altered tumors
Anti-PD-1 + MEK/STAT3 inhibitor	PD-1 + MEK/STAT3	PDAC with inflamed TME	Phase I/II	Converts immunologically cold TME; ongoing
Dietary fructose reduction / KHK-C inhibition	KHK-C enzyme	PDAC prevention in high-sugar contexts	Preclinical	Genetic KHK-C ablation improves survival in KPC mice

10. FUTURE DIRECTIONS

The mechanistic paradigm established by Hu et al. (2019) and subsequently reinforced by studies in KRAS mouse models (Sato et al., 2020; Chung et al., 2020) opens several critical translational research avenues. First, the O-GlcNAcylation-RRM1-KRAS mutagenesis pathway identifies OGT as a potential chemoprevention target; the development of pancreas-specific OGT inhibitors with suitable pharmacokinetic profiles for chronic administration in high-risk diabetic individuals—analogous to the use of metformin—could reduce the incidence of KRAS mutations in pre-malignant pancreatic tissue. However, the pleiotropic roles of O-GlcNAcylation in normal cellular homeostasis (transcription, translation, chromatin remodeling) necessitate careful preclinical evaluation of tissue specificity and toxicity before clinical translation.

Second, the specific link between dietary fructose and KRAS-MAPK pathway amplification through KHK-C establishes dietary modification as a mechanistically grounded chemopreventive intervention in high-risk populations. Prospective intervention trials examining whether reduction of sugar-sweetened beverage consumption, specifically targeting free fructose intake, reduces progression of existing PanIN lesions or KRAS mutation burden in ctDNA from high-risk individuals (those with familial PDAC, KRAS-positive pancreatic cystic lesions, or new-onset DM) would provide direct translational evidence for public health dietary recommendations. Third, the development of non-invasive biomarker strategies—plasma ctDNA KRAS mutation detection, O-GlcNAc-modified protein signatures in urine or serum, and HBP metabolomics panels—could enable identification of high-risk individuals in the pre-invasive PanIN stages when surgical cure is most feasible. Integration of these biomarkers with AI-driven clinical risk scores for new-onset DM patients would substantially improve the positive predictive value of screening programs. Fourth, the immunological consequences of KRAS inhibitor-driven TME remodeling (demonstrated with MRTX1133) provide a

strong rationale for combination trials of KRAS G12D inhibitors with immune checkpoint inhibitors in KRAS G12D PDAC, particularly in patients whose tumors exhibit cGAS-STING pathway activation secondary to metabolic stress-induced DNA damage in the hyperglycemic context. Finally, whether optimized glycemic control in existing T2DM patients reduces PDAC incidence through attenuation of the O-GlcNAcylation-KRAS mutagenesis pathway represents an addressable hypothesis that could be examined in large prospective cohort studies linking granular glycemic control metrics (HbA1c trajectories, glucose variability) with PDAC incidence endpoints.

11. CONCLUSION

The relationship between high sugar intake, diabetes mellitus, and KRAS-mediated pancreatic carcinogenesis has evolved from a statistical epidemiological association to a mechanistically characterized molecular pathway of profound biological and clinical significance. The central molecular nexus linking chronic hyperglycemia to pancreatic carcinogenesis is the hexosamine biosynthesis pathway: high glucose concentrations elevate intracellular UDP-GlcNAc levels and promote OGT-mediated O-GlcNAcylation of ribonucleotide reductase, depleting dNTP pools and inducing genomic instability that preferentially generates de novo KRAS G12D mutations in pancreatic cells. Once established, oncogenic KRAS G12D rewires cellular metabolism through the Warburg effect, HBP upregulation, PPP activation, and glutamine scavenging—programs that are further amplified by the hyperglycemic and hyperinsulinemic environment of DM, creating a self-reinforcing oncogenic metabolic cycle. Downstream signaling through RAF/MEK/ERK, PI3K/AKT/mTOR, and JAK-STAT3 pathways drives PanIN progression to invasive PDAC, orchestrates the immunosuppressive desmoplastic tumor microenvironment, and confers resistance to conventional systemic therapies. Dietary fructose compounds these effects through KHK-C-mediated KRAS-MAPK amplification and mTORC1 co-activation. Translational implications are substantial: metformin and dietary sugar restriction may attenuate the O-GlcNAcylation pathway and reduce KRAS mutagenesis in high-risk individuals; enriched PDAC surveillance strategies in carefully defined new-onset DM populations could enable earlier diagnoses when surgical cure is achievable; and the recently developed KRAS G12D-targeted inhibitors—MRTX1133 and ASP3082—hold promise for the dominant KRAS mutation specifically linked to hyperglycemia-driven mutagenesis. Together, these advances establish the high sugar–diabetes–KRAS axis as a fundamental paradigm for understanding and intercepting PDAC carcinogenesis.

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