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Review Article

Metabolic reprogramming in diabetes and cancer: the role of PI3K/AKT/mTOR and beyond

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Abstract: Diabetes mellitus and cancer are among the most prevalent chronic diseases worldwide, and accumulating evidence suggests a significant association between these conditions. The metabolic disturbances characteristic of diabetes, including hyperglycemia, hyperinsulinemia, insulin resistance, and chronic inflammation, create a favorable environment for tumor initiation and progression. These alterations contribute to cellular metabolic reprogramming, enhanced proliferative signaling, and resistance to apoptosis. Key molecular pathways such as PI3K/AKT/mTOR, along with dysregulated glucose, lipid, and amino acid metabolism, play central roles in linking diabetic and oncogenic processes. In addition to metabolic alterations, genetic and epigenetic modifications, including mutations in oncogenes and tumor suppressor genes, as well as the involvement of non-coding RNAs, further strengthen this association. Emerging evidence also highlights the gut microbiome's role in modulating inflammation, metabolic homeostasis, and cancer susceptibility in diabetic conditions. Therapeutically, antidiabetic agents such as metformin, GLP-1 receptor agonists, and SGLT2 inhibitors have shown potential in modulating cancer-related pathways, although clinical evidence remains variable and requires further validation. This review provides a comprehensive overview of the shared metabolic and molecular mechanisms underlying the diabetes-cancer link, emphasizing the interplay between metabolic dysregulation, genetic alterations, and microbiome dynamics. A better understanding of these interconnected pathways may support the development of targeted therapeutic strategies and improve clinical outcomes. However, further well-designed studies are necessary to establish causal relationships and translate these findings into effective clinical interventions.

Keywords: Diabetes, epigenesis, hyperglycemia, insulin resistance, neoplasms

Introduction

Diabetes mellitus and cancer are the most prevalent and challenging chronic diseases affecting the global population. The incidence of both conditions has increased significantly over the past few decades, posing a substantial burden on healthcare systems worldwide. By 2021, it is estimated that between 529 million adults in the world were living with diabetes, and the rate of prevalence is expected to keep rising sharply, especially in low-income and middle-income nations [1]. At the same time, cancer was listed among the most common causes of morbidity and mortality, with almost 10 million cases dying, and more than 18 million cases were newly diagnosed each year [2]. This combination of the two states is especially alarming, as people with type 2 diabetes mellitus (T2DM) are at a very high risk of getting a range of malignancies, including hepatocellular carcinoma, pancreatic ductal adenocarcinoma, colorectal cancer, breast cancer (particularly, postmenopausal type), and endometrial cancer, which have a relative risk increased by 1.2- to 2.5-fold in relation to the site of the cancer [3, 4].

Epidemiological data strongly prove the increased risk of cancer and worse prognosis in patients with diabetes despite the presence of shared risk determinants of disease like obesity and lack of physical activity [5]. This relationship is further supported by pathological and mechanistic studies that indicate that chronic hyperglycemia and hyperinsulinemia, insulin resistance and low-grade systemic inflammation in diabetes precondition a permissive met-

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abolic environment that actively favor oncogenic transformation, tumor progression, and poorer clinical outcomes [6, 7]. The rationale for studying diabetes and cancer in the context of metabolic pathology is compelling. Persistent hyperglycemia and hyperinsulinemia in T2DM predispose individuals to persistent oncogenic pathways (e.g., PI3K-AKT-mTOR), induce Warburg-like metabolic programs, epigenetic memory formation, and alter the gut microbiome, thereby contributing to tumor formation and growth [8, 9]. This is not just comorbidity by association, and in fact, diabetes forms a systemic pro-tumorigenic environment by having direct effects on cellular energetics, immune surveillance and tissue remodeling. Recent mechanistic and translational studies are growing to support the view that diabetes is a causal factor that can be modified, rather than an active co-factor [10]. However, a unified mechanistic framework integrating metabolic and signaling crosstalk remains lacking. The purpose of this review is to discuss the pathway level mechanism of how diabetic induced metabolic stress initiates and progresses cancer, to assess the causal evidence of human pathology, experimental model and translational studies, to discuss the therapeutic opportunities of antidiabetic agents and metabolic regulators to prevent and treat cancer in diabetic patients, and to determine the role of diabetes related gut dysbiosis. The review enhanced molecular and translational pathology and will help future efforts to develop precision-based prevention and intervention strategies to mitigate the increasing number of people living with type 2 diabetes who are at increased risk of cancer comorbidity.

Pathological basis of metabolic reprogramming in diabetes and cancer

The Pathological Basis of Metabolic Reprogramming in Diabetes and Cancer is one of the fundamental connections on why diabetes leaves individuals susceptible to cancer development and progression. Dysregulated cellular metabolism has traditionally been considered an atypical feature of cancer. Chronic hyperglycemia, insulin resistance, and hyperinsulinemia, especially T2DM, profoundly alter cellular energy metabolism and nutrient utilization [11]. These alterations are similar to much of what has been found in cancer cells, where metabolic reprogramming contributes to high proliferation rates, stress tolerance, and adaptation to adverse microenvironmental conditions [12]. The point of convergence lies in increased glucose uptake and reliance on aerobic glycolysis (Warburg effect). However, it is also accompanied by equally important alterations, including hyperinsulinemia-driven activation of P13K-AKT-mTOR axis, which promotes anabolic processes and cell growth, dysregulated lipid metabolism characterized by increased de novo lipogenesis and impaired β-oxidation leading to lipotoxicity increases glutamine dependency and one-carbon metabolism that help in nucleotide synthesis and epigenetic modification and persistent oxidative stress that induces DNA damage and genomic instability. In diabetic tissues, hyperglycemia contributes to increased glucose influx through increased expression of transporters (e.g., GLUT1 and GLUT4 in some cases), whereas hyperinsulinemia increases mTOR signaling and lipid production. Collectively, these interconnected alterations generate elevated lactate production, mitochondrial dysfunction, chronic inflammation, and oxidative stress, thereby creating a permissive environment that supports oncogenic and tumor progression [13]. This dysregulation is further demonstrated by distinct histopathological and molecular signatures. Chronic low-grade inflammation, ectopic lipid accumulation (lipotoxicity), mitochondrial dysfunction, and oxidative damage are found in diabetic tissues, particularly in the liver (nonalcoholic fatty liver disease progression), pancreas (β-cell exhaustion and fibrosis), adipose tissue (adipocyte hypertrophy with macrophage infiltration), and epithelial sites (e.g., colon and breast) [14]. The tissue-specific susceptibilities underscore the fact that diabetes increases the risk of cancer in certain organs. Insulin-mediated lipogenesis and inflammation predispose the liver to high-risk hepatocellular carcinoma, β-cell stress and ductal adenocarcinoma promotion through hyperinsulinemia affects the pancreas, dysfunction in adipose tissues promotes systemic inflammation and tumor growth via adipokines, and hyperinsulinemia promotes DNA damage and epigenetic changes in the epithelial tissues (colon and breast) [15, 16]. The convergent pathways of these changes include PI3K-AKT-mTOR, Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB)-mediated inflammation, and oxi-

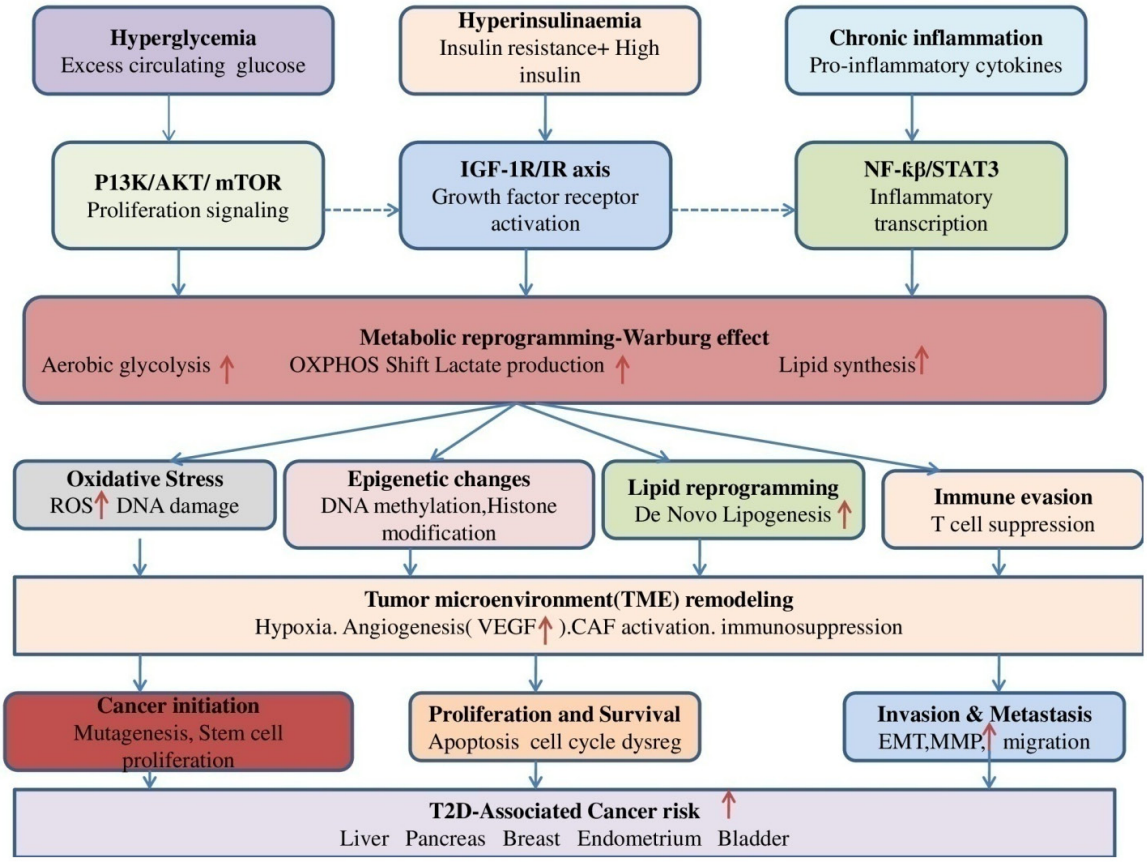

Figure 1. Type 2 diabetes-driven metabolic reprogramming that promotes cancer initiation and progression.

dative-stress-induced genomic instability, which take cells to a state of cancer-prone condition (**Figure 1**). Although most studies support these connections, some findings conflict with the causal and correlational claims. A few Mendelian randomization studies have hinted at direct causal effects of hyperglycemia and hyperinsulinemia on site-specific cancers, but a variety of others have suggested that there are confounding effects of obesity or overlapping causal actions [17]. Speculative theories postulate that the insulin-resistance-driven Warburg-like rearrangement of diabetic tissues might be an adaptation to mitochondrial dysfunction rather than a primary oncolytic trigger, with controversies over the sequence of events: whether insulin resistance occurs before or after glycolytic changes [12, 18]. These need to be addressed through longitudinal human pathology that incorporates multi-omics.

One of the key hallmarks that connect diabetes and cancer is altered cellular metabolism, and the diabetic tissues were profoundly reprogrammed through increased aerobic glycolysis, dysfunctional mitochondria, lipotoxicity, and continual oxidative stress. All these histopathological and molecular markers of steatosis and fibrosis in the liver, β-cell dedifferentiation and inflammation in the pancreas, adipose tissue bio-crown-like structures and hypertrophic adipose epithelial cells, epithelial remodeling and DNA damage in colon and breast generate the pro-tumorigenic microenvironment that actively predisposes diabetic tissues to malignant transformation.

Convergent metabolic pathways driving disease progression

Insulin/IGF-1 signaling and PI3K-AKT-mTOR axis

Hyperinsulinemia in T2DM is an essential oncogenic driver, overstimulating the insulin/IGF-1 receptor axis, leading to activation of the PI3K-AKT-mTOR pathway, which inhibits growth, survival, proliferation, metastasis, and apoptosis

in premalignant and cancerous cells [19, 20]. A critical mechanistic feature underlying this effect is the paradox of selective insulin resistance. Insulin resistance most often affects the metabolic arm of insulin action in classical insulin target tissues (liver, skeletal muscle, and adipose tissue), leading to a decrease in the ability to take up glucose and also to a failure to inhibit hepatic gluconeogenesis [21]. By contrast, other components of the insulin signaling pathway, such as the mitogenic (growth-promoting) pathway through the PI3K-AKT-mTOR pathway, are largely preserved or hyperactive in epithelial and premalignant cells [22]. This selectivity is brought about by the continued strong stimulation of IRS-1/IRS-2 and downstream PI3K signaling, resulting in sustained AKT phosphorylation and mTORC1 activation that promotes anabolic metabolism and proliferation, despite blunted glucoregulatory responses [23, 24]. Elevated insulin thus establishes a pro-tumorigenic state that differs from normal, with a strong bias in the direction of driving oncogenic signaling, and in which systemic metabolic control is lost [25].

Increased insulin and IGF-1 levels stimulate their receptors on target cells, causing IRS-1/2 to be phosphorylated and leading to the recruitment of insulin-dependent lipid kinase (PI3K), which activates AKT, and activates mTORC1, increasing protein synthesis, glycolysis, and uptake of nutrients (**Table 1**) [25]. It is supported by evidence from patient samples, cell culture and animal models that this mechanism is driven by diabetes. Hyperinsulinemia T2DM patients show a positive association between p-AKT, p-mTOR levels and insulin resistance markers, as well as a higher risk of developing site-specific cancers such as colorectal, liver and endometrial [26, 27]. High insulin exposure in cell culture results in hepatocellular cancer signal transduction, which leads to upregulation of GLUT1 and HK2 through the activation of AKT [28]. Hyperinsulinemia is observed before accelerated tumor development in the case of constitutive activation of the PI3K-AKT-mTOR pathway in obese/diabetic mouse models (db/db or high-fat diet), which can be reversed by insulin-sensitizing agents [10, 25].

Although the pathway is supported by strong preclinical and epidemiological evidence, there is also some observational evidence pointing towards residual confounding due to obesity, but there is growing evidence from Mendelian randomization studies that this pathway is directly causal for liver and pancreatic cancers (**Table 1**) [29, 30].

Glucose metabolism and aerobic glycolysis

Hyperglycemia and insulin resistance seen in diabetes increase glucose uptake and glycolytic flux in susceptible tissues, which aids biosynthetic needs for the initiation and progression of tumors [31, 32]. This metabolic switch shares characteristics with the Warburg effect seen in cancer cells, but is exaggerated in the diabetic environment with the upregulation of important transporters and enzymes [33]. Some important enzymes include GLUT transporters, HK2, and PKM2. GLUT1/4 is overexpressed such that it permits the maintenance of glucose uptake in insulin-resistant adipocytes and tumor cells, and was stabilized by HIF-1α, which upregulates HK2 to trap glucose, in cases of diabetic liver and cancer [34]. PKM2 dimeric form channels intermediates to serine production and nucleotide formation, which is exaggerated in the proliferative diabetic tissues and tumors [35]. The diabetic patient-derived xenografts have an increased PKM2 expression, which is related to rapid growth [36]. It has been proposed that this metabolic shift may initially represent an adaptive response to insulin resistance but becomes oncogenic under chronic stress; however, causality remains debated, with some studies suggesting context-dependent roles of PKM2 [32] (**Table 1**).

Lipid metabolism and fatty acid signaling

The dyslipidemia associated with diabetes, the development of non-alcoholic fatty liver disease (NAFLD), and dysfunction of adipose tissue are the factors that promote an aberrant de novo lipogenesis and the change of β-oxidation to supply lipids to tumor membrane biogenesis, oncogenic signaling, and fatty acid oxidation dependency of cancer cells [16, 37]. Insulin activates lipogenesis through SREBP-1c in liver and adipose tissue, leading to excess fatty acid production that can be exploited by premalignant cells [38] (**Table 1**). There is a dominant adipose-tumor cross-talk, where maladaptive, dysfunctional adipose in T2DM emits free fatty acids which activate PPARγ to trigger metastasis in breast and prostate models, and NAFLD

Table 1. Key metabolic pathways by which diabetes drives cancer progression

Key Metabolic Pathway	Principal Molecular Mediators	Affected Tissues	Supporting Evidence	Diabetes Cancer direction	References
Aerobic Glycolysis (Warburg Effect)	GLUT1, HK2, PFK, PKM2, LDHA, HIF-1α, c-Myc	Liver, pancreas, breast, colorectal, endometrium	Human: Upregulated glycolytic enzymes in tumors from diabetic patients; hyperglycemia correlates with increased lactate in biopsies. Cell culture: High glucose levels enhance proliferation and lactate production in cancer cell lines. Animal: Hyperglycemic/diabetic mice show accelerated tumor growth via glycolytic shift.	The aerobic glycolysis increases due to hyperglycemia and insulin resistance, which provide the biosynthetic precursors for tumor growth	[10, 59]
PI3K/AKT/mTOR Signaling	PI3K, AKT, mTORC1, IRS-1, IGF-1R	Pancreas, breast, liver, prostate, colorectal	Human: Hyperactivation in diabetic cancers; hyperinsulinemia linked to poor prognosis. Cell culture: Insulin stimulates AKT/mTOR promoting survival/proliferation. Animal: Insulin-resistant models exhibit enhanced tumor progression via mTOR hyperactivity.	Hyperinsulinemia in T2DM drives excessive activation, promoting proliferation, survival, and metastasis in premalignant cells.	[10, 116]
Insulin/IGF-1 Signaling	Insulin receptor (IR), IGF-1R, IRS proteins	Breast, endometrium, prostate, liver	Human: Elevated circulating insulin/IGF-1 in T2DM is associated with higher cancer risk/mortality. Cell culture: Hyperinsulinemia drives anabolic signaling and epithelial-mesenchymal transition. Animal: Obese/diabetic models show IGF-1-mediated tumor promotion.	Chronic hyperinsulinemia and elevated IGF-1 in diabetes directly stimulate oncogenic receptor signaling and tumor progression.	[20, 59]
AMPK Suppression and Energy Sensing	AMPK (inhibited), mTOR (activated)	Liver, pancreas, adipose, muscle	Human: Reduced AMPK activity in diabetic tissues and tumors. Cell culture: Excess glucose suppresses AMPK, thereby enhancing mTOR-driven biosynthesis. Animal: AMPK knockout or diabetic models accelerate oncogenesis via unbalanced energy signaling.	Hyperinsulinemia inhibits AMPK, leading to unchecked anabolic metabolism that favors tumor initiation and growth.	[117, 118]
Hexosamine Biosynthetic Pathway (HBP) and AGE Formation	GFAT, O-GlcNAc transferase, RAGE	Liver, pancreas, breast, vasculature	Human: Increased O-GlcNAcylation and AGEs in diabetic complications and tumor microenvironments promote inflammation/oxidative stress. Cell culture: High glucose fluxes into HBP, enhancing protein modification and proliferation. Animal: Diabetic models show HBP-driven inflammation accelerating tumorigenesis.	Chronic hyperglycemia generates AGEs that bind RAGE, driving ROS and inflammation that promote carcinogenesis.	[10, 119]
Chronic Inflammation and Oxidative Stress	NF-κB, IL-6, TNF-α, ROS, JNK	Colon, liver, breast, adipose	Human: Elevated inflammatory markers in T2DM patients with cancer; ROS-linked DNA damage in biopsies. Cell culture: Hyperglycemia induces NF-κB activation and ROS. Animal: High-fat diet/diabetic mice exhibit inflammation-driven tumor initiation.	Low-grade inflammation and ROS overproduction in diabetes act as a pathological bridge, inducing genomic instability and tumor initiation.	[51, 120]

T2DM, Type 2 Diabetes Mellitus; GLUT1, Glucose Transporter 1; HK2, Hexokinase 2; PFKP, hosphofructokinase; PKM2, Pyruvate Kinase M2; LDHA, Lactate Dehydrogenase A; HIF-1α, Hypoxia-Inducible Factor 1-alpha; c-Myc, Cellular Myelocytomatosis Oncogenem; TOR, Mechanistic Target of Rapamycin; FAT, Fatty Acid Translocase (CD36); OGT, O-GlcNAc Transferase; RAGE, Receptor for Advanced Glycation End-products; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor alpha; ROS, Reactive Oxygen Species; JNK, c-Jun N-terminal Kinase.

offers a lipid-rich niche to hepatocellular carcinoma (HCC) [39, 40]. Lipid accumulation due to impaired β-oxidation in diabetes induces compensatory responses in tumors, including increased CPT1A expression to maintain energy and redox balance [41]. Diabetic NAFLD patients exhibit elevated ACC and FASN expression, reflecting lipogenic features similar to those in HCC [28]. However, variability in fatty acid oxidation dependence across tumors and tumor microenvironments remains a limitation, with some studies suggesting that de novo lipogenesis predominates in advanced cancers [42] (**Table 1**).

Amino acid and one-carbon metabolism

Amino acid metabolism and one-carbon metabolic pathways play critical roles in cellular homeostasis and are frequently dysregulated in metabolic disorders such as diabetes and cancer. These pathways contribute to tumor growth by supporting biosynthesis, redox balance, and epigenetic regulation. In a hyperglycemic and insulin-resistant environment, alterations in nucleotide synthesis, redox balance, and epigenetic remodeling contribute to oncogenic transformation [43, 44]. GLS1 is increased in stressed diabetic tissues to carry out glutaminolysis to restore TCA intermediates during glycolytic diversion [45] (**Table 1**). Serine provides units through the folate cycle to produce SAM, which affects the methylation of DNA/histones [46, 47]. Hyperglycemia disrupts the balance between SHMT/PHGDH, resulting in changes in the methylation of oncogenes; cancers use this to proliferate [48]. High-glucose/insulin cell models trigger MTHFD2, which is a reflection of tumor metabolic auxotrophy [49]. These pathways are highly context-dependent; for example, serine uptake may compensate under glutamine-limited conditions, while the persistence of epigenetic alterations in diabetic environments remains under investigation [50].

Chronic inflammation and oxidative stress

Chronic low-grade inflammation and oxidative stress induced by diabetes lead to a vital pathological connection to cancer. Excess reactive oxygen species (ROS) production triggered by hyperglycemia through NF-κB, JAK (Janus Kinases)-STAT (Signal Transducers and Activators of Transcription), and NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome signaling, is persistently involved in DNA damage, genomic instability, and the initiation of tumors [51, 52]. Adipose tissue expansion and macrophage infiltration in T2DM lead to the release of tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6), which activate NF-κB and JAK-STAT in premalignant cells [53] (**Table 1**). NLRP3 perceives ROS stress in diabetes, which induces the release of IL-1β, insulin resistance and tumor angiogenesis [28]. Excess production of mitochondrial ROS leads to DNA damage, genomic instability, and the development of cancer, and 8-oxoguanine lesions are increased in diabetic tissues and tumors [25]. High CRP/IL-6 levels are associated with increased disease progression in comorbid patients, as shown in patient samples [36]. It remains unclear whether this relationship is causal or reflects shared underlying factors (e.g., obesity), although there are cases in which it is considered secondary in models [52] (**Table 1**).

Altogether, convergent metabolic pathways discussed insulin/IGF-1-driven PI3K-AKT-mTOR hyperactivation, hyperglycemia-driven Warburg-like aerobic glycolysis, dysregulated lipid metabolism with de novo lipogenesis and fatty acid oxidation dependence, increased glutamine and serine-glycine/one-carbon flux to biosynthetic and epigenetic functions, as well as chronicity low-grade inflammation and oxidative stress, can be seen to demonstrate how. These pathways do not just coexist in diabetic and cancerous tissues, but instead diabetes-induced perturbations (chronic hyperglycemia, hyperinsulinemia, insulin resistance, dyslipidemia, and systemic inflammation) form a permissive, pro-tumorigenic environment that facilitates oncogenic transformation, tumor growth, tumor invasion, tumor metastasis and resistance to therapy of vulnerable organs including the liver, pancreas, colon, breast, and endometrium.

This diabetes-to-cancer directionality is confirmed by a strong patient cohort (increased pathway activation with insulin resistance markers), mechanistic cell culture (to simulate high-glucose/high-insulin conditions), and preclinical diabetic (i.e. db/db mice or high-fat diet rodents) model evidence. Although a few con-

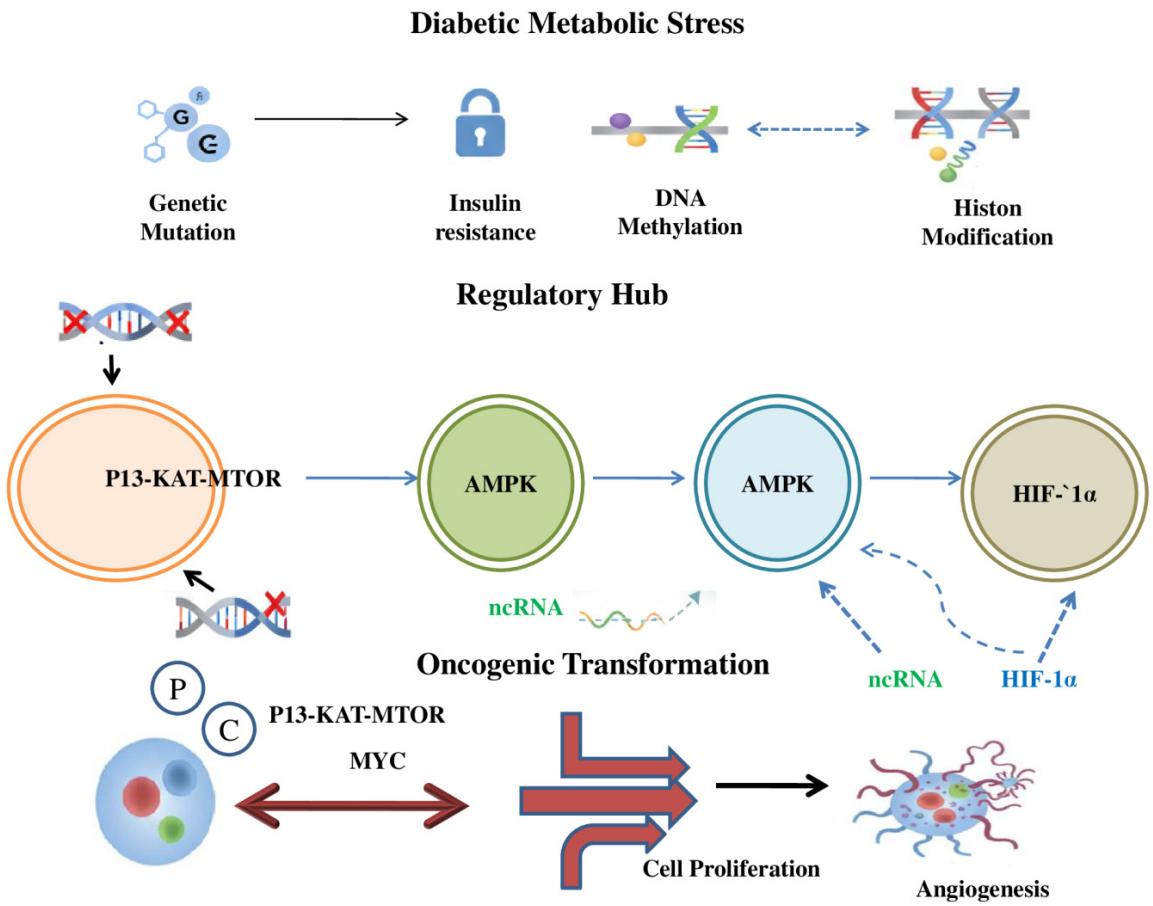

Figure 2. Molecular genetics and epigenetic alterations by which diabetes promotes carcinogenesis.

flating observations may still remain, e.g. residual obesity confounding in observational data, context-dependent enzyme activities (e.g., PKM2 or FAO variability), or causality versus correlation debates in Mendelian randomization studies, emerging mechanistic and translational studies are increasingly finding supporting evidence that diabetes is a causal variable and not merely a comorbidity. The potential to prevent and treat these common nodes is significant. Antidiabetic agents (e.g., metformin, sodium-glucose cotransporter 2 (SGLT2) inhibitors, GLP-1 receptor agonists), which reduce hyperinsulinemia, hyperglycemia, and inflammation, have demonstrated anticancer effects in preclinical studies and more recent clinical studies, with repurposed metabolism modulators (e.g., PI3K/AKT/mTOR or glutaminase inhibitors) having the potential to disrupt diabetes-promoting oncogenic signaling. Further, treatment of upstream factors such as obesity and gut dysbiosis can help discontinue this metabolic cascade.

Molecular genetic alterations linking metabolism, diabetes, and carcinogenesis

Molecular and genetic alterations play a critical role in linking metabolic dysregulation in diabetes with carcinogenesis, influencing key signaling pathways, cellular metabolism, and tumor progression. Metabolic dysregulation caused by diabetes favors the changes in the molecular genetics between hyperglycemia, hyperinsulinemia, and insulin resistance to carcinogenesis. Among them are oncogenic hyperactivation, inactivation of tumor suppressors, epigenetic restructuring, and non-coding RNA dysregulation that break the homeostasis of metabolism, cause genomic instability, and leave a heritable pro-oncogenic state gene in diabetic tissues [46, 48, 54] (**Figure 2**).

Oncogenes and tumor suppressors with metabolic functions

Oncogenic signaling pathways have intrinsic metabolic functions that are influenced by

hyperinsulinemia and hyperglycemia, which is due to diabetes, that rewires energy circuits to promote proliferation and survival in premalignant cells [55]. MYC amplification that is found in diabetes-related HCC, and in pancreatic ductal adenocarcinoma (PDAC) promotes a hyperglycemic stress-induced glutaminolysis, nucleotide synthesis, and Glycolytic enzyme upregulation of Glycolytic enzyme upregulation (HK2, LDHA) to sustain biosynthetic needs. Oncogenic KRAS mutations, which are increased in diabetic PDAC, also promote glucose uptake through GLUT1 and redirect intermediates to hexosamine production to support glycosylation and signaling [56]. PIK3CA-stimulating changes hyperstimulate AKT/mTOR that emulates chronic insulin signaling and induces lipogenesis through SREBP-1 and anabolic metabolism [57]. Diabetes-associated metabolic dysfunction also impairs key tumor-suppressive metabolic checkpoints, increasing tissue vulnerability. In the insulin-resistant liver, PTEN inactivation deregulates PI3K/AKT signaling, promoting lipogenesis, ROS accumulation, and tumor growth [58]. TP53 mutation, which is common in cancers associated with diabetes, disrupts AMPK activation and mitochondrial quality control, thereby maintaining Warburg-like metabolism and genome instability [59]. LKB1/STK11 loss disrupts energy sensing through AMPK, obesity/T2DM to lung and cervical cancer, among other effects, including mTOR hyperactivity and metabolic adaptation [60, 61]. These changes undermine metabolic restraint within the diabetic milieu setting up tissues to undergo oncogenic remodeling. However, contradictory evidence persists regarding whether checkpoint loss (e.g., PTEN or TP53 inactivation) is a cause or consequence of metabolic stress in diabetes-associated cancer. Additionally, tissue-specific effects (e.g., liver vs. pancreas) and residual confounding from obesity complicate the interpretation of observational data [16].

Epigenetic remodeling driven by metabolic stress

In diabetes, chronic metabolic stress leads to epigenetic remodeling by changing the availability of metabolites to DNA methylation, histone modifications and chromatin accessibility to establish lasting pro-oncogenic patterns of gene expression [62]. Hyperglycemia increases the pools of acetyl-CoA and SAM, which induce histone acetylation (e.g., H3K9ac, H3K27ac) as well as abnormal DNA methylation that inhibits tumor suppressors (e.g., p16 4 in diabetic pancreas) and activates oncogenes [63]. One prime example is the epigenetic imprinting of hyperglycemia: a short-term high glucose level induces sustained alterations (e.g. H3K9me3 of NF-κB targets, global hypomethylation with focal hypermethylation) that are long-term maintained after the acute normalization of glycemic control, which drive inflammation, oxidative stress and pro-tumorigenic signaling in endothelial, epithelial and renal cells [48, 64]. Similar remodeling of MYC/HIF-1α super-enhancers in cancer settings enhances glycolysis and metabolic plasticity. The kidneys of diabetic individuals are hypomethylated at oncogenes that drive renal cell carcinoma formation, and fat tissue is depleted of H3K27me3 at the PPARγ loci, which facilitates breast cancer metastasis, liver/epithelial tissue is persistently inflammatory/epigenetically activated, attaching NAFLD to HCC [64]. These inherited changes hasten the evolution in a comorbid case. There is speculation that epigenetic memory can be in part reversible (e.g. through the control of TET enzymes or HDAC inhibitors), although persistence through cell division and causation in human cohorts is controversial [65].

Non-coding RNAs in metabolic regulation

Non-coding RNAs (ncRNAs) such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) have proven to be important regulators that mediate diabetic metabolic stress and oncogenic transformation. The lncRNAs like H19 and MALAT1 are more expressed in diabetic conditions and promote the oncogenic signaling by sponging tumor suppressive miRNA or recruiting epigenetic regulators like EZH2 [66].

These changes in ncRNA are of particular interest because they mediate the connection between upstream diabetic metabolic stress and downstream cancer hallmarks. NcRNAs that are dysregulated by diabetes directly regulate metabolic regulators (PI3K/AKT/mTOR, HIF-1alpha, MYC) or alter epigenetic memory, and the pro-oncogenic state is maintained in a self-reinforcing loop even following partial glycemic control. They are also promising non-

invasive biomarkers to identify diabetic people with diabetes who are at high risk of developing cancer due to their stability in circulation. ncRNAs serve as biomarkers for diabetes-associated cancer risk and targets for precision interventions. Context-dependency (protective and oncogenic functions) and the delivery dilemma are among the most critical issues; tissue-specific networks in diabetes-cancer crosstalk need to be further validated.

The discussed components of molecular genetic changes, oncogenic hyperactivation with metabolic rewiring (MYC, KRAS, PIK3CA driving glutaminolysis, glycolysis, and lipogenesis), loss of major tumor suppressors and checkpoints, hyperglycemia-induced epigenetic reprogramming with a non-resolving metabolic memory. Such changes do not occur spontaneously in cancer but, conversely, they are actively induced, enhanced, and maintained through chronic diabetic metabolic stress (hyperglycemia, hyperinsulinemia, insulin resistance, and oxidative/inflammatory burden) into a heritable, pro-oncogenic cellular response that promotes tumor initiation, progression, invasion, metastasis, and treatment resistance in high-risk tissues (liver, pancreas, breast, colon, kidney, and endometrium). Not only do the epigenetic memory and ncRNA-mediated circles existing post-partial glycemic recovery reveal oncogenic price-paid over time, but also actionable therapeutic windows are emphasized through reversible factors (e.g., through metabolic or epigenetic modulators). Evidence from clinical cohorts, mechanistic studies, and multi-omics analyses supports diabetes as a causal factor in carcinogenesis. These insights highlight the therapeutic potential of targeting metabolic, epigenetic, and ncRNA pathways, as well as the use of ncRNA-based biomarkers for risk stratification. Finally, viewing diabetes as a systemic metabolic stressor provides a unified framework for understanding its link to cancer and supports integrated translational strategies to reduce disease burden.

Drug-mediated modulation of diabetes-driven metabolic pathways in cancer prevention and therapy

Various antidiabetic agents have been investigated not only for glycemic control but also for their potential effects on cancer-related pathways. Direct and indirect anticancer effects are observed when antidiabetic agents that correct upstream metabolic stressors are used, whereas shared nodes are used with revolved metabolic modulators. Some obstacles are patient heterogeneity, resistance mechanisms, and the need to use precise approaches [67-69].

Antidiabetic drugs with anti-cancer implications

Antidiabetic drugs, beyond their primary role in glycemic control, have emerged as potential modulators of cancer risk and progression through their effects on metabolic and signaling pathways [70, 71] (**Figure 3**). The most studied is metformin, which acts through inhibiting mTORC1 by enabling AMPK, which suppresses protein synthesis and glycolysis, decreases insulin/IGF-1 signaling, thereby suppressing cell proliferation, and anabolic metabolism [72]. It also helps in reducing the circulating insulin and IGF-1 levels, inhibition of P13K-mTOR signaling caused by hyperinsulinemia may enhance tumor growth and other anticancer effects are the induction of apoptosis and cell cycle arrest (mainly G0/G1 phase by upregulating p53/p21), induction of autophagy by activating ULK1, and alleviation of chronic inflammation and oxidative stress. All of these effects interfere with the pro-tumorigenic metabolic environment that diabetes generates [59] (**Figure 3**). Complementary mechanisms have also been noted to suppress cancer with other antidiabetic drugs. SGLT2 inhibitors decrease the availability of glucose in the body, as well as inflammation, resulting in a reduction in tumor mass and enhancement of metabolic trajectories in diabetic mouse models [73]. GLP-1 receptor agonists cause weight loss, increase insulin sensitivity, and inhibit NF-κB-mediated inflammation, and are particularly effective against obesity-induced cancers such as colorectal and endometrial cancer [74]. These agents work together to activate several nodes of diabetes-induced carcinogenesis- such as hyperinsulinemia, hyperglycemia, lipotoxicity and chronic inflammation as opposed to a single pathway [75] (**Figure 3**).

Metabolic considerations for diabetic patients receiving cancer therapy

Metabolic considerations are critical in diabetic patients undergoing cancer therapy, as

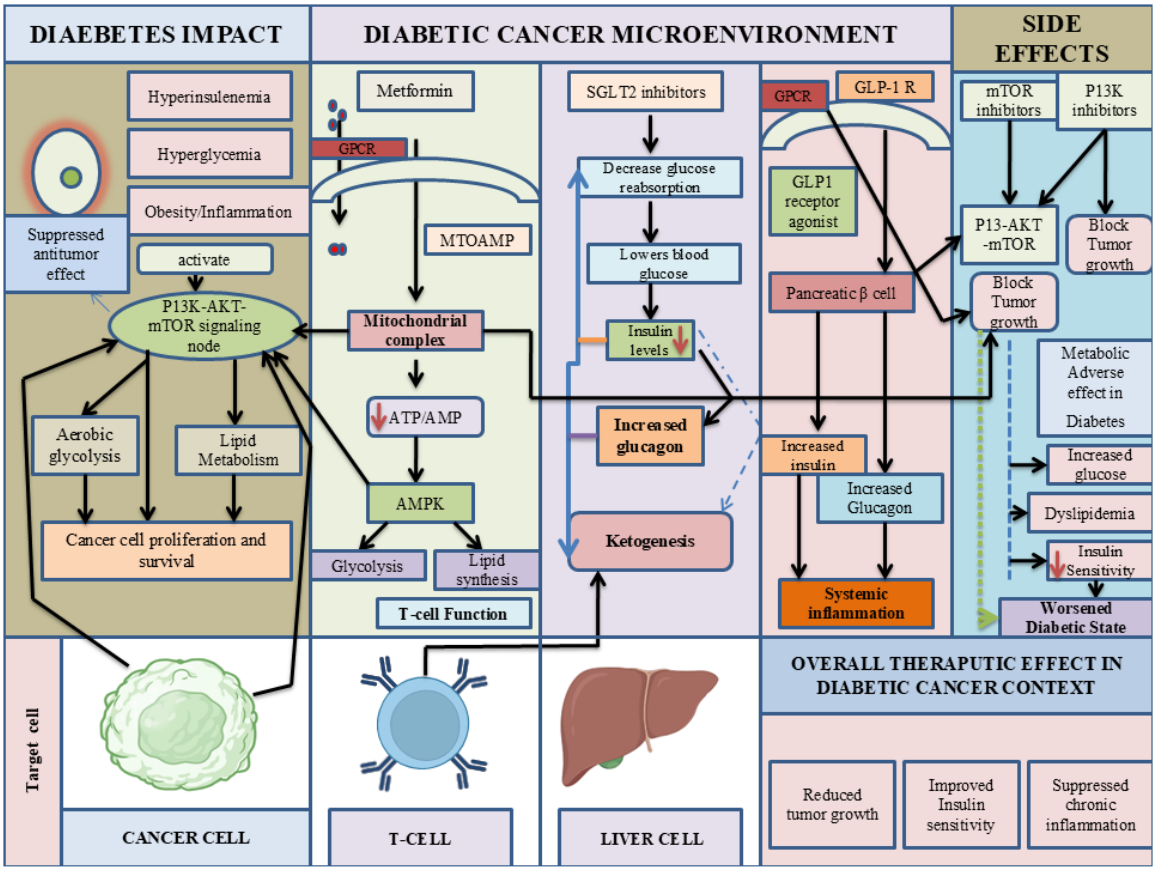

Figure 3. Drug-mediated modulation of diabetes-driven metabolic pathways in cancer prevention and therapy.

anticancer treatments can significantly disrupt glucose homeostasis and metabolic balance. Cancer therapies, including chemotherapy, targeted therapy, and immunotherapy, can alter metabolic pathways, leading to complications such as hyperglycemia, insulin resistance, and metabolic instability. Chemotherapeutic agents may influence glucose metabolism either directly or indirectly by inducing stress responses, inflammation, and altered insulin sensitivity [76]. Glucocorticoids, frequently used as adjuncts in cancer therapy, represent a major contributor to metabolic disturbances. These agents increase hepatic gluconeogenesis and reduce peripheral glucose uptake, leading to steroid-induced hyperglycemia. Such effects can exacerbate pre-existing diabetes and increase the risk of acute metabolic complications [77]. Anticancer therapies may have a profound effect on metabolic activity and tend to worsen underlying diabetes mellitus, which is a significant clinical caveat despite the main focus of the current review being on upstream diabetes modulation to prevent cancer [59, 74].

Hyperglycemia (grade 3-4 in most instances) is often caused or aggravated by targeted therapies, especially PI3K/AKT/mTOR inhibitors (e.g. alpelisib and everolimus) through the inhibition of insulin signaling and the enhancement of insulin resistance. This on-target effect replicates and exacerbates the metabolic derangements that already exist in T2DM, and could contribute to residual tumor growth by increasing glucose availability [78, 79]. mTOR inhibitors are also capable of inducing dyslipidemia by stimulating lipogenesis via SREBP, and this complicates metabolism control in diabetic patients [80]. Traditional chemotherapy drugs have other metabolic effects. Platinum compounds and taxanes induce insulin resistance by oxidative stress and systemic inflammation, whereas anthracyclines affect mitochondrial 8 oxidation, causing lipotoxicity and energy imbalances [81]. Hyperglycemia is strongly induced by glucocorticoids (e.g., dexamethasone), which are often used during chemotherapy; they stimulate hepatic gluconeogenesis and inhibit it in 20-30% of patients.

Such metabolism changes are very intense among patients with existing diabetes, which usually leads to worse glycemic control [76, 82]. Pathological implications of diabetes are significant in patients. Hyperglycemia induced by anticancer therapy may enhance tumor promotion by diabetes, enhance the probability of acute metabolic crises (e.g., diabetic ketoacidosis or hyperosmolar state), amplify treatment-related toxicity, and even decrease the overall effectiveness of therapy. These interactions emphasize close metabolic surveillance, a timely dose change of anticancer and antidiabetic medications, and multidisciplinary care of oncologists and endocrinologists [74] (**Table 2**).

Repurposing metabolic modulators for cancer prevention and therapy

Diabetes-related cancers can be prevented and autonomously treated by repurposing metabolic modulators as an adjunct to the recommended antidiabetics, and these assertions may be demonstrated through preclinical models and pharmacological research [67, 69]. Metformin inhibits tumor formation in the diabetic/obese animals; cross-clinical trials investigating adjuvant utility in breast/colorectal cancer are underway. SGLT2-inhibitors delay NAFLD-HCC and renal anticancer signal-based models. Other modulators (e.g., glutaminase inhibitors to reduce glutamine dependency, dichloroacetate to reverse the Warburg effect, FAO blockers like etomoxir) have been shown not only to exhibit anti-diabetes robustness by blocking common nodes in other biological contexts (**Table 2**). The groups of diabetics at high risk can enjoy the advantages of early metabolic correction to halt the oncogenic reprogramming. The adjunctive use improves immunotherapy/sensitivity in comorbid patients. However, several limitations remain, including tumor heterogeneity, potential off-target effects, lack of large randomized controlled trials specifically in diabetic populations, and the need for validated predictive biomarkers. To sum up, the therapeutic manipulation of metabolic mechanisms triggered by diabetes using drugs can mark a new era of translational research on the most effective way to stop the causal relationship between type-2 diabetes and cancer. Antidiabetic medications, in particular metformin, SGLT2 inhibitors, and GLP-1 receptor agonists, have become first-line candidates not only for glycemic management but also for cancer prevention and as adjunctive therapy in diabetes. These agents interfere with the upstream signaling pathways in hyperglycemia, hyperinsulinemia, insulin resistance, chronic inflammation, and oxidative stress, inhibiting tumor initiation, tumor progression, and poor outcomes in tissues with increased risk, thereby attenuating the upstream signaling in PI3K/AKT/mTOR, IGF-1, and reversing Warburg-like metabolic reprogramming, decreasing lipogenesis and glutamine dependency.

Recent clinical evidence consistently shows a 20-40% risk reduction in site-specific cancers in treated diabetic cohorts. Mechanistic preclinical models show reversal of the diabetes-fueled hallmark in xenografts, db/db mice, and high-fat diet systems. These are greatest when interventions are delivered at an early stage of the diabetic pathway, which identifies a window of primary preventive intervention in prediabetic or newly diagnosed patients with a high risk profile of cancer progression. Although therapy of cancer can induce metabolic stress among diabetic patients, these are ancillary effects that signify the necessity of combined oncologic-endocrinologic care without subtracting the primary preventive action of metabolically correcting patients with diabetes. The ability to repurpose other metabolic modulators expands their therapeutic applications, especially as adjunctive therapy to cancers linked to diabetes or preventive therapy in high-risk subgroups. Nonetheless, there are still limitations: tumor heterogeneity and resistance mechanisms, off-target toxicity, variable efficacy in non-diabetic or advanced-stage settings, lack of validated biomarkers to stratify patients and monitor their responses, and no validated biomarkers for the indications.

It will be necessary to fill these gaps with precision trials to improve patient selection via multi-omics, combination therapy, and long-term longitudinal studies in diabetic patients. Finally, antidiabetic and metabolic drugs should be repositioned as cancer-preventive or disease-modifying agents, an inexpensive and accessible way of reducing the dual burden of type 2 diabetes and malignancy. This informed approach confirms diabetes as not only a

Table 2. Metabolic drugs influencing diabetes-cancer crosstalk: molecular targets and pathological outcomes

Drug/Class	Primary Metabolic Targets	Experimental Models Used	Observed Pathological or Anticancer Outcomes	References
Metformin (Biguanides)	AMPK activation; mTOR inhibition; mitochondrial complex I disruption; IGF-1 signaling modulation	Cell lines (breast, lung, prostate); animal xenografts; RCTs/meta-analyses; observational cohorts	Reduces proliferation/apoptosis induction; lowers risk/mortality in colorectal, breast, prostate, liver cancers; enhances chemotherapy sensitivity	[68, 121]
SGLT2 Inhibitors (e.g., Dapagliflozin, Empagliflozin)	SGLT2 inhibition (glycosuria); anti-inflammatory (↓TNF-α/IL-6); insulin sensitivity improvement; IGF signaling modulation	Cell lines (lung, pancreatic); animal models; retrospective cohorts; RCTs/meta-analyses	Reduces overall tumor incidence (esp. lung/ovarian); longer progression-free/overall survival; improved metabolic profiles in T2D-cancer patients	[122, 123]
GLP-1 Receptor Agonists (e.g., Liraglutide, Semaglutide)	GLP-1R activation; insulin secretion enhancement; glucagon suppression; weight loss; PI3K/AKT/mTOR inhibition	Cell lines (prostate, colorectal); animal models (NASH/HCC); RCTs/meta-analyses; cohort studies	Neutral overall risk; reduces obesity-related/prostate/colorectal/liver cancers; potential thyroid risk (mixed); apoptosis induction	[123, 124]
Thiazolidinediones (TZDs, e.g., Pioglitazone)	PPAR-γ activation; insulin sensitivity improvement; inflammation/oxidative stress reduction	Cell lines (breast, lung); animal models; observational/meta-analyses	Mixed: Reduces breast/hepatocellular risk; potential bladder cancer concern (inconsistent); anti-proliferative via cyclin degradation	[69, 125]

mTOR, Mechanistic Target of Rapamycin; IGF-1, Insulin-like Growth Factor 1; SGLT2, Sodium-Glucose Cotransporter 2; TNF-α, Tumor Necrosis Factor alpha; IL-6, Interleukin-6; GLP-1R, Glucagon-like Peptide-1 Receptor; NASH, Non-Alcoholic Steatohepatitis; HCC, Hepatocellular Carcinoma; PPAR-γ, Peroxisome Proliferator-Activated Receptor gamma.

comorbidity, but a modifiable trigger of carcinogenesis, clearing the road to combined metabolic-oncologic approaches that would undoubtedly have a significant impact on reducing cancer incidence and cancer mortality in the rising global population with diabetes.

Microbiome-driven regulation of diabetes-induced metabolic dysregulation and carcinogenesis

The gut microbiome functions as an endocrine metabolic organ, which can play an important role in controlling host metabolism and tumor biology [83]. Dysbiosis in patients with T2DM disturbs this process, producing microbial metabolites and immune responses that exacerbate hyperglycemia, insulin resistance, low-grade chronic inflammation, and oncogenic pathways, triggering an increased cancer risk and progression [9, 84, 85] (**Table 3**).

Gut microbiota as a metabolic endocrine organ

Microbial metabolites are the focus of regulating insulin sensitivity and inflammation in the diabetic environment. Enteroendocrine and immune cells respond to short-chain fatty acids (SCFAs) or butyrate, acetate, and propionate produced by fiber-fermenting bacteria, which activate G-protein-coupled receptors (GPR41/43 and GPR109A) [86]. This activates the secretion of GLP-1 and PYY, increases insulin sensitivity, inhibits appetite, and has strong anti-inflammatory mechanisms through HDAC inhibition and NF-κB suppression [9] (**Table 3**). Conversely, the choline metabolite of trimethylamine N-oxide (TMAO), and secondary bile acids (launched by dysbiosis like deoxycholic acid) are pro-inflammatory metabolites and, as demonstrated in diabetes-associated dysbiosis, trigger NLRP3 inflammasome, increase hepatic gluconeogenesis, and contribute to overall systemic insulin resistance [87]. Impaired intestinal barrier integrity (so-called leaky gut), lipopolysaccharides (LPS) translocation, and low-grade endotoxemia are caused by reduced abundance of beneficial SCFA producers (e.g., Faecalibacterium prausnitzii, Roseburia, and Akkermansia muciniphila). This maintains the inflammation triggered by the NF-κB and exacerbates the diabetic condition, which provides a supportive condition for carcinogenesis [9, 85] (**Table 3**). In T2DM, bile acid pools are altered, which are caused by diminished microbial conversion to secondary bile acids, and interfere with FXR and TGR5 signaling, exacerbating lipid metabolism and hepatic inflammation, leading to the development of HCC [88].

Microbiome-cancer-diabetes axis

Gut dysbiosis, linked to diabetes, directly regulates immune surveillance and carcinogenesis via microbial metabolites and bacterial products. Low levels of SCFA affect Treg differentiation and IL-10 synthesis, thereby promoting the protumorigenic response of Th17 cells and chronic inflammation [89]. Pathobionts like Fusobacterium nucleatum, which is enriched in patients with diabetes, activate Wnt/b-catenin signaling via the FadA adhesin and promote the progression of colorectal cancer (CRC) [90]. The secondary bile acids (deoxycholic acid) and LPS also promote the DNA damage and epithelial-to-mesenchymal transition in the liver and colon [84]. Germ-free and antibiotic-treated animal models are of strong causal evidence. Germ-free diabetic mice that are colonised with faecal microbiota of T2DM donors have faster colorectal tumor development, colorectal tumor burden, through more deoxycholic acid and inflammatory colonic disease. Depletion of beneficial taxa by antibiotics (e.g., Akkermansia) in high-fat diet diabetic models aggravates steatohepatitis and tumor progression, which is partially mitigated by fecal microbiota transplantation (FMT) of lean donors or addition of SCFA-producing bacteria [9, 91]. These models reveal that dysbiosis induced by diabetes is not only correlated but also promotes oncogenic signaling and prevents antitumor immunity.

Translational implications and therapeutic opportunities

Microbiome-based interventions have significant potential to disaggregate the diabetes-cancer axis. Healthy donor-to-T2DM fecal microbiota transplantation (FMT) has been observed to enhance insulin sensitivity and systemic inflammation in T2DM patients, and preclinical data show that concomitant tumor growth is slowed by restoration of SCFA and barrier effects [92]. Probiotics (Akkermansia muciniphila), prebiotics (inulin-type fructans), and postbiotics (butyrate analogs) positively

Table 3. Microbiome-derived metabolites linking metabolic dysfunction to cancer-related pathology

Major Microbial Metabolite	Host Targets	Metabolic and Inflammatory Effects	Evidence from Clinical Studies and Experimental Models	References
Short-Chain Fatty Acids (SCFAs: Butyrate, Propionate, Acetate)	GPR41/43/109A receptors; HDAC inhibition; PPARγ activation	Reduced SCFA levels impair insulin sensitivity, gut barrier integrity, and anti-inflammatory signaling (IL-10↑, NF-κB↓)	Clinical: Lower fecal SCFAs in T2DM patients correlate with higher CRC and HCC risk. Experimental: SCFA supplementation or FMT restores barrier function and suppresses tumor-promoting inflammation in a diabetic mouse model	[70, 126]
Secondary Bile Acids (e.g., Deoxycholic Acid, Lithocholic Acid)	FXR/TGR5 receptors (dysregulated); EGFR; NF-κB pathway	Increased levels induce lipotoxicity, oxidative stress, DNA damage, and pro-inflammatory cytokine production	Clinical: Elevated deoxycholic acid in T2DM patients with NAFLD correlates with HCC and CRC progression. Experimental: High-fat diet diabetic models show accelerated hepatocarcinogenesis via bile acid-induced inflammation	[10, 127]
Trimethylamine N-Oxide (TMAO)	PERK/FoxO1 pathway; NLRP3 inflammasome	Elevates systemic inflammation, endothelial dysfunction, and insulin resistance; fosters pro-tumorigenic microenvironment resistance; fosters pro-oncogenic chronic low-grade inflammation	Clinical: Higher plasma TMAO in T2DM strongly associates with increased cancer incidence and mortality. Experimental: TMAO supplementation in diabetic mice promotes colorectal and liver tumor growth	[128, 129]
Indole Derivatives (e.g., Indole-3-Propionic Acid)	AhR (aryl hydrocarbon receptor); PXR	Dysregulated (often reduced) levels impair immune regulation, barrier function, and promote chronic inflammation and oncogenic signaling	Clinical: Reduced indole metabolites in T2DM-CRC overlap. Experimental: AhR activation by indole metabolites suppresses tumor progression in diabetic animal models	[70, 130]

AMPK, AMP-activated Protein Kinase; mTOR, Mechanistic Target of Rapamycin; IGF-1, Insulin-like Growth Factor 1; SGLT2, Sodium-Glucose Cotransporter 2; GLP-1R, Glucagon-like Peptide-1 Receptor; SCFAs, Short-Chain Fatty Acids; HDAC, Histone Deacetylase; PPARγ, Peroxisome Proliferator-Activated Receptor gamma; T2DM, Type 2 Diabetes Mellitus; CRC, Colorectal Cancer; HCC, Hepatocellular Carcinoma; FMT, Fecal Microbiota Transplantation; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; FXR, Farnesoid X Receptor; TGR5, Takeda G Protein-Coupled Receptor 5; EGFR, Epidermal Growth Factor Receptor; PERK, Protein Kinase R-like Endoplasmic Reticulum Kinase; FoxO1, Forkhead Box Protein O1; TMAO, Trimethylamine N-Oxide; ROS, Reactive Oxygen Species.

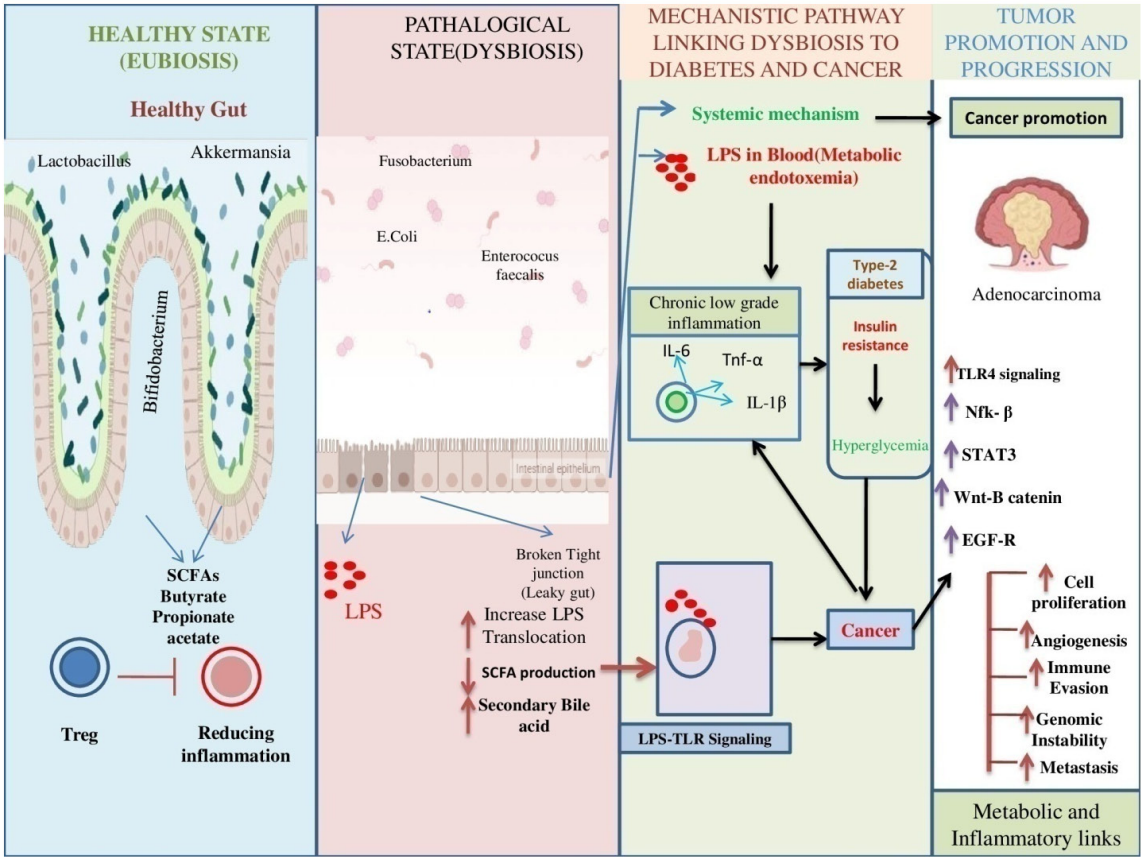

Figure 4. The microbiome-diabetes-cancer axis.

affect the maintenance of intestinal health, reduce NF-κB signaling and hinder cancer-promoting inflammation in diabetic animal models [84, 93] (**Figure 4**).

Notably, a number of antidiabetic agents exert some of their effects by altering the intestinal microbiota, boosting SCFA production and decreasing pathobiont levels, which may also hint at synergistic effects of both pharmacological and microbiome-based interventions. The issues of clinical translation are still a problem. They include donor variability, variable rates of engraftment (especially in immunosuppressed cancer patients), the risk of bacteremia or pathogen transmission, and a lack of long-term efficacy data. The key unresolved problems are the incompleteness of heterogeneity of the microbiome composition among diabetic subjects, the absence of common protocols, and the necessity of high-scaled randomized controlled trials in diabetic high-risk cancer subjects [9, 94]. The next phase in the strategy is likely to entail individualized metagenomic profiling and combination therapies to fully utilize the microbiome to prevent diabetes-related cancer.

The gut microbiome is an important mediator in the causal pathway linking T2DM to increased cancer risk. Dysbiosis linked to diabetes alters the gut microbiota of a healthy metabolically endocrine organ into a metabolically deranged, inflammatory, and immune-surveillance-impaired, oncogenic signaling driver. An imbalance of pro-inflammatory metabolites: Diabetic dysbiosis promotes carcinogenesis, notably in the liver, colon, and pancreas through a permissive microenvironment, leading to reduced production of protective short-chain fatty acids (SCFA), increased presence of pro-inflammatory metabolites (TMAO, secondary bile acids), and increased intestinal permeability (**Figure 4**).

There is compelling evidence of diabetes-induced microbial changes not only being traditional correlational, but also actively promoting

tumor progression and initiation, through alterations of immune activity, the functioning of the intestinal barrier, and metabolic-driven signaling, in germ-free and antibiotic-treated, and fecal microbiota transplantation (FMT) models. There is also human observational and interventional evidence that this axis can be improved by restoring microbial balance and, by so doing, can enhance insulin sensitivity and reduce inflammation-associated cancer risk. Microbiome-targeted therapies, such as FMT, selective probiotics (Akkermansia muciniphila), prebiotics, postbiotics, and dietary interventions, have the potential to support conventional antidiabetic treatments by way of adjunctive therapies. Interestingly, some antidiabetic medications (metformin, SGLT2 and GLP-1 receptor agonists) already have a proportion of their positive effects through microbiota modulation, implying a possibility of synergistic effects.

Nonetheless, clinical translation is faced with serious challenges. These are variability of donors, variable engrafting, and safety issues in immunocompromised cancer patients, strain effect, and absence of large-scale or long randomized studies specifically targeting diabetic populations who are at high risk of cancer. The complexity of standardization is also complicated by the heterogeneity in the composition of individual microbiomes and the complex interactions between diet, drugs and host genetics. In the future, a combination of metagenomic profiling and multi-omics will be necessary in order to create personalized microbiome-based interventions. Such approaches might suppress the origins of the metabolic-immune-oncogenic cascade by targeting the underlying pathogenesis of diabetes-related maladies, providing a new preventive and curative modality to mitigate the morbidity of malignancies, and could ultimately lower the incidence of diabetes-related malignancies. This microbiome-centric view supports the use of a comprehensive, pathway-scale conceptualization of diabetes as an adjustable contributor to cancer, leading to combination metabolic and microbial therapies in personalized oncology.

Experimental models supporting causal pathogenesis from diabetes to cancer

The use of experimental models is essential in demonstrating causal factors between the metabolic disorder caused by diabetes and the development of cancer. These systems present mechanistic information and translational support that diabetes is a preventable stimulus of tumor development and progression by replicating key characteristics of chronic hyperglycemia, hyperinsulinemia, insulin resistance, and dysbiosis in controlled settings [95]. Reductionist in vitro systems Versatile *in vivo* models' Multifactorial human T2DM: Each of these levels has its distinct advantages and disadvantages in trying to capture the chronic, multifactorial nature of the disease.

Invitro models

Cell culture systems are effective in modelling the direct effects of diabetic glucose stress, diabetic insulin stress, or diabetic palmitate stress on tumorigenesis because they can be subjected to a high-glucose, high-insulin environment, or a high-palmitate, diabetic environment. Hepatocyte lines (e.g., HepG2) incubated with hyperinsulinemia promote SREBP-1c-mediated lipogenesis and have a Warburg-type metabolism, which mimics early events of NAFLD progression to HCC [96]. In high-glucose media, pancreatic acinar or ductal cells develop endoplasmic reticulum stress, β-cell dedifferentiation and acinar-to-ductal metaplasia in the form of both 3D organoids [97]. Diabetic-like conditions lead to increased PI3K/AKT/mTOR activation, elevated proliferation, and increased glycolytic flux of breast (MCF-7) and colorectal (HCT116) cancer cells, which are blocked by metformin or SGLT2 inhibitors [28, 98].

Advantages of in vitro models are that individual variables are tightly controlled (e.g. glucose concentration, insulin levels), that they allow high-throughput screening of metabolic modulators, and that they have the ability to mechanistically dissect key oncogenes (MYC, KRAS) or tumor suppressors (PTEN, TP53) [99]. Compared with 2D cultures, 3D organoids and spheroids are more successful at recapitulating tissue architecture and hypoxic gradients. Monocultures do not have systemic factors, immune cells, and stromal interactions of the tumor microenvironment. Short models do not always capture the chronic features of human diabetes, and findings can overestimate the dependence on Warburg effects or the effectiveness of drugs [100]. Patient-derived organ-

oids from diabetic patients are becoming increasingly physiologically relevant systems, though they still need to be validated with *in vivo* data.

In vivo and animal models

In vivo and animal models play a pivotal role in elucidating the mechanistic interplay between diabetes-induced metabolic dysregulation and cancer development. These models provide critical insights into key pathological processes such as insulin resistance, hyperglycemia, hyperinsulinemia, and metabolic reprogramming, which collectively contribute to tumor initiation and progression. In vivo models provide an important systemic background to establish that diabetes is a predisposing factor that causally encourages the development of cancer [6]. The diabetic animal models are uniquely configured to mimic the major metabolic changes noticed in human T2DM in the absence of tumor induction. High fat diet (HFD) feeding evokes obesity, insulin resistance, hyperinsulinemia, and long-term chronic low-grade inflammation, which is highly reminiscent of the human T2DM metabolic environment. The use of streptozotocin (STZ) with or without HFD results in the partial destruction of 3/4 of the 3/4-pth of the pancreatic islets, resulting in hyperglycemia and insulin deficiency/resistance, which allows researchers to compare the isolated or combined actions of hyperglycemia and hyperinsulinemia on carcinogenesis [36]. Upon subsequent challenge with chemical carcinogens (e.g., diethylnitrosamine [DEN] to induce hepatocellular carcinoma or azoxymethane/dextran sulfate sodium [AOM/DSS] to induce colorectal cancer), such diabetic models invariably show accelerated tumor formation and progression at the expense of hyperinsulinemia and hyperglycemia [101, 102].

Researchers use more and more combined models of diabetes-cancer in order to understand the complex human disease condition. These involve the implantation of cancer cell lines or patient-derived xenografts into diabetic hosts (e.g. Stz-treated or db/db mice) [103]. Through these models, it is possible to study the simultaneous changes in the effect the diabetic metabolic environment has on tumor growth, tumor metastasis, and tumor therapy response in a living system characterized by systemic insulin resistance, hyperglycemia, dyslipidemia and altered inflammatory phenotype. As an example, breast or colorectal cancer xenografts proliferate better in diabetic versus normoglycemic mice; there is increased angiogenesis, and resistance to apoptosis, which is a direct indication of the tumor-promoting impact of the diabetic milieu [9].

Mechanistic knowledge is further enhanced through genetic models. Leptin-deficient (ob/ob) or leptin receptor-deficient (db/db) mice naturally develop NAFLD-NASH-HCC progression, and tissue-specific knockouts (e.g., PTEN or LKB1 liver deletion on a diabetic background) for loss of metabolic checkpoints have been found to increase oncogenic signaling in insulin-resistant circumstances [104, 105]. Microbiome-modulated systems like those with germ-free diabetic mice colonized with microbiota of T2DM patients have demonstrated to expedite colitis-related cancer and HCC through a reduction in SCFA production and an increase in secondary bile acids reversible by FMT of healthy donors [9, 84]. Advantages of such animal models are that they can be used to investigate long-term, systemic metabolic effects, tumor longitudinal growth, and interventional testing (e.g., tumor promotion reversal using metformin or SGLT2 inhibitors). Limitations consist of the difference in metabolism and lifespan under species, faster disease progression than human chronic diabetes, and the possibility of overestimating some pathways because of inbred strains.

Human pathology and translational evidence

The best form of direct translation validation is in human tissue-based molecular pathology studies. Monitoring biopsies and surgical specimens from diabetic patients with NAFLD or prediabetes regularly reveals elevated p-AKT, SREBP-1c, and glycolytic enzymes (HK2, LDHA, PKM2) in both non-cancerous and tumorous tissues, mirroring findings in diet-induced diabetic mouse models. The β-cell dead space, GLUT2 neutering, and the nearby ductal metaplasia with early KRAS phenotypes promote the development of diabetic metabolic stress into pancreatic ductal adenocarcinoma [106]. Causal inference in a clinical cohort is strengthened when it is combined with experimental

data. Longitudinal study and Mendelian randomization on the relationship between prediabetic hyperinsulinemia and hyperglycemia, and multi-omics profiling (transcriptomics, metabolomics, spatial transcriptomics) of diabotumor tissues demonstrates the association between site-specific cancer occurrence and prediabetic cancer depending on activation of the pathway (PI3K/AKT/mTOR) or remodelling of epigenetics [17]. PDX prepared in diabetic mice and human organoids conditioned to hyperglycemic culture also fill the gap and show sustained responses to the metabolic treatments metformin and SGLT2 inhibitors [107]. Human studies have high clinical relevance but face difficulties assessing temporal causality due to confounding factors (obesity, medications, comorbidities) and inadequate longitudinal sampling of tissues. Still, the overall evidence from *in vitro*, *in vivo*, and human pathology models suggests that diabetes is a causal factor in metabolic reprogramming and carcinogenesis [108].

There is substantial evidence that, at different levels, experimental models are being used to offer strong evidence that diabetes is a causal factor behind carcinogenesis by causing long-lasting metabolic reprogramming. It can be shown through in vitro systems that hyperglycemia and hyperinsulinemia can cause oncogenic signaling, glycolytic changes, and epigenetic changes directly in normal and transformed cells. The *in vivo* models, especially in diet-induced diabetic mice and microbiome-manipulated systems, demonstrate convincingly that diabetes is the precursor and enhancer of tumor initiation and progression in high-risk tissues, including liver, pancreas and colon. These data are further supported by human pathology and studies on translational model systems, which show similar molecular patterns (e.g. PI3K/AKT/mTOR hyperactivation, increased epigenetic aerobic glycolysis, and long-lasting epigenetic memory) in the tissues of diabetic patients that recapitulate the findings with experimental models.

The overlapping of the results of cell culture, genetically engineered and diet-induced animal models, germ-free/FMT systems, patient-derived organoids, and clinical tissue studies favorably point towards directional causality of metabolic stress caused by diabetes to cancer progression. These models have contributed to the deconstruction of major mechanisms, such as hyperinsulinemia-induced PI3K-AKT-mTOR signaling, hyperglycemia-induced aerobic glycolysis, and microbiome-mediated inflammation, and have also been essential in the preclinical testing of preventive and therapeutic interventions, such as metformin, SGLT2 inhibitors. Combining the results of these experimental platforms, the researcher is able to achieve a higher level of causality and assess the efficacy of interventions in metabolism, and these interventions are expected to break the loop of carcinogenesis caused by diabetes. Mechanistic understanding is further refined using genetic models. NAFLD-NASH-HCC progression in leptin-deficient (ob/ob) or leptin receptor-deficient (db/db) mice occurs spontaneously, and tissue-selective knockouts (e.g. PTEN deletion or LKB1 deletion in the liver on a diabetic background) indicate how attenuation of metabolic checkpoints enhances oncogenic signaling in an Microbiome-engineered probes, including germ-free diabetes mice inoculated with microbiota of T2DM patients, show enhanced colitis-related cancer and hepatic cancer through lowering SCFA levels and elevating secondary bile acids, which are partially ended by FMT of healthy donors.

The advantages of these animal models are that it is possible to examine long-term systemic metabolic effects, longitudinally develop tumors, and perform interventional testing (e.g. reversal of tumor promotion by metformin or SGLT2 inhibitors). Changes in metabolism and lifespan across species, the speed of disease progression relative to human chronic diabetes, and the possibility that some pathways are overestimated by inbred strains are among the limitations. However, every model system has its limitations. In vitro models lack systemic and microenvironmental complexity; animal models tend to develop disease faster and are not metabolically similar to humans; and human studies face barriers to strict temporal causality due to confounding factors and the ethical challenge of the length of a longitudinal study. To overcome these gaps, a higher mode of integration of new technologies (such as spatial multi-omics, humanized mouse models harboring diabetic microbiota and long-term patient-derived organoid platforms) will be necessary to model diseased situations in chronic

diabetic patients. Finally, the cumulative data obtained in these test models support the idea that diabetes is not a just a comorbidity but is a manipulable metabolic phenotype, which drives a pro-tumorigenic environment. This etiological model provides a solid basis for formulating specific preventive mechanisms and also supports the argument for reusing antidiabetic and metabolic agents to curb disease-induced carcinogenesis at its initial stage.

Knowledge gaps and future directions in understanding diabetes as a causal driver of cancer

There has been significant progress in understanding the relationship between metabolic stress associated with diabetes and the development of cancer, but there remain key gaps in our understanding which hinder strong causal inferences and clinical translation. There are many limitations of the current evidence, including the fact that most studies in humans are retrospective and are confounded by obesity, medications, and lifestyle. There is limited longitudinal data on the transition from prediabetes to malignancy, which is difficult to assess the exact role and order of each of the factors, hyperinsulinemia, hyperglycemia, chronic inflammation and gut dysbiosis. Furthermore, most experimental models do not reflect the chronic, heterogeneous nature of type 2 diabetes in humans over the course of decades [6, 109].

There are still unanswered questions about the exact mechanisms connecting diabetes and cancer. These include the relative contribution of individual diabetic metabolic stressors (such as hyperinsulinemia, hyperglycemia, chronic inflammation, and gut dysbiosis) to the development of different cancer types, the extent to which hyperglycemia-induced epigenetic memory persists and remains reversible, the causal role of diabetes-associated microbiome alterations in human carcinogenesis, and the identification of reliable biomarkers capable of stratifying cancer risk among patients with T2DM [70, 110, 111].

Future research needs focus on several important directions in order to help fill these knowledge gaps. To characterize the temporal sequence of metabolic dysfunction to malignancy, large-scale prospective longitudinal cohorts with serial multi-omics profiling (spatial transcriptomics, metabolomics, and epigenomics) urgently require to be set up, starting from the prediabetic stage [112]. Simulating chronic diabetic conditions in patient-derived organoids and humanized mouse models containing diabetic patient microbiota will be important for the development of more accurate mechanistic studies [113]. Furthermore, properly designed interventional trials are needed to measure the cancer-preventive efficacy of antidiabetic drugs and therapies targeting the microbiome in high-risk diabetic individuals [114]. Lastly, the use of artificial intelligence and systems biology will be crucial to combine multi-layered data, to forecast the progression from diabetes to cancer and to enable personalized approaches to diabetes prevention [115].

Conclusions

Metabolic reprogramming is a key and potentially reversible process that contributes to the initiation, progression, and poor clinical outcomes of cancer. Chronic hyperglycemia, hyperinsulinemia, insulin resistance, low-grade inflammation, oxidative stress, and diabetes-associated dysbiosis of the gut all create a pro-tumorigenic milieu that actively promotes oncogenic transformation in multiple tissues, such as the liver, pancreas, colon, breast and endometrium.

This review has shown that diabetes is not just associated with cancer, but also acts as an upstream cause due to the sustained activation of important pathways including PI3K-AKT-mTOR, increased glycolytic flux, dysregulated lipid metabolism, amino acid and one-carbon metabolism, epigenetic remodeling, and dysregulation of non-coding RNA. The gut microbiome also exacerbates this risk through the production of different metabolites that affect immune surveillance and inflammation. These mechanisms can be understood in a pathway based and microbiome informed approach and present a number of potential therapeutic targets.

Antidiabetic drugs, especially SGLT2 inhibitors, GLP-1 receptor agonists, and metformin, have the potential to act as dual agents to correct underlying metabolic derangements and inhibit processes linked to cancer. These strategies, coupled with microbiome targeted inter-

ventions, offer novel opportunities for precision prevention and adjunctive therapy in high-risk populations with diabetes. This shift in perspective, shifting from treating diabetes as a comorbidity to a modifiable risk factor for cancer, will require a paradigm shift in clinical practice. There is a need for future studies to focus on longitudinal multi-omics-driven studies, models with relevance to humans, and personalized prevention trials to convert these insights into effective strategies. Significant decreases in cancer burden in patients with diabetes can be achieved by addressing diabetes-associated metabolic vulnerabilities at their root, which will have a positive impact on millions of patients around the world.

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Disclosure of conflict of interest

None.

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