

O-GlcNAcylation as an emerging molecular target for cholangiocarcinoma therapy (Review)

PURIN CHAROENSUKSAI^{1,2} and SIWANON JIRAWATNOTAI³⁻⁵

¹Department of Biomedicine and Health Informatics, Faculty of Pharmacy, Silpakorn University, Nakhon Pathom 73000, Thailand;

²Research and Innovation Center for Advanced Therapy Medicinal Products, Faculty of Pharmacy, Silpakorn University, Nakhon Pathom 73000, Thailand; ³Siriraj Center of Research Excellence for Precision Medicine and Systems Pharmacology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand; ⁴Department of Pharmacology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand; ⁵Faculty of Pharmacy, Silpakorn University, Nakhon Pathom 73000, Thailand

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Abstract. Aberrant O-GlcNAcylation and the upregulation of O-GlcNAc transferase (OGT) are key contributors to cancer pathogenesis and progression, driving hyperproliferative states and metastatic phenotypes. Targeting OGT may suppress cancer progression, positioning OGT and O-GlcNAc signaling as compelling targets in cancer research. Cholangiocarcinoma (CCA), a rare yet highly aggressive malignancy of the bile duct system, represents a clinical challenge, underscored by its rising global mortality, poor survival outcomes and high recurrence rate, despite advances in awareness, diagnostics and therapeutic strategies. Consequently, there is need for novel therapeutic modalities. Hyperactive O-GlcNAcylation and upregulation of OGT are observed in CCA, therefore, targeting protein O-GlcNAcylation may have clinical potential. The present review aimed to summarize the impact of O-GlcNAcylation on CCA and CCA-relevant hallmarks of cancer including cell proliferation, metastasis, metabolic reprogramming, angiogenesis, programmed cell death and tumor-associated inflammation. In areas where direct evidence in CCA is limited, insights from other gastrointestinal tract cancers may identify potential mechanistic connections, offering a broader context to guide future investigation. Furthermore, the viability of OGT and O-GlcNAcylation as therapeutic targets is discussed.

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1. Introduction

O-linked- β -N-acetylglucosaminidation or O-GlcNAcylation is a form of protein post-translational modification involving the attachment of N-Acetyl-D-glucosamine to serine or threonine residues of cell proteins (1). The addition and removal of O-GlcNAc moieties are the function of two key enzymes, O-GlcNAc transferase (OGT) (2-4) and O-GlcNAcase (OGA) (5,6), respectively.

The human OGT gene is located on the X chromosome at Xq13.1, near the centromere (Fig. 1A) (7). This gene contains 23 exons and 21 introns, which undergo alternative splicing to produce three distinct protein isoforms, each differing primarily in its N-terminal region: Nucleocytoplasmic OGT (ncOGT), mitochondrial OGT (mOGT) and short form OGT (sOGT). ncOGT, the longest isoform, consists of 1,046 amino acids and is derived from exons 1-4 and 6-23 (Fig. 1A and B) (8,9). The second longest, mOGT, comprises 931 amino acids encoded by exons 5-23. This isoform is uniquely characterized by a mitochondrial targeting sequence at its N-terminus (10). The shortest isoform, sOGT, contains 675 amino acids, derived from exons 10-23 (8).

The crystal structure of OGT proteins reveals two main domains: N-terminal tetratricopeptide repeat (TPR) motifs and the C-terminal catalytic region, connected by a nuclear localization sequence (3,11). While all three OGT isoforms share the same C-terminal catalytic region, they exhibit notable structural differences in their N-terminal TPR motifs (Fig. 1B). ncOGT, mOGT and sOGT contain 13, 9 and 2 TPRs, respectively (Fig. 1B) (12). The N-terminal TPRs are organized into a helical structure (Fig. 1C) and are crucial for protein-protein interactions, as well as binding of OGT substrates (12). OGT typically denotes the full-length ncOGT (~110 kDa) which

Correspondence to: Dr Siwanon Jirawatnotai, Department of Pharmacology, Faculty of Medicine Siriraj Hospital, Mahidol University, 12th Floor, Srisawarindhira Build, Bangkok 10700, Thailand
E-mail: siwanon.jir@mahidol.ac.th

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is the predominant variant responsible for the majority of O-GlcNAcylation activity in mammalian cells (13-15).

Uridine diphosphate N-acetylglucosamine (UDP-GlcNAc), serving as the GlcNAc donor molecule, is generated from the hexosamine biosynthesis pathway (HBP), a branch metabolic pathway from glycolysis (Fig. 2A). A total of 2-5% of glucose uptake by cells is channeled through HBP (16). The processing of glucose in the HBP involves the conversion of fructose-6-phosphate to glucosamine-6-phosphate by glutamine fructose-6-phosphate amidotransferase (GFAT, Fig. 2B), the first rate-limiting step of the HBP pathway (17,18). To produce UDP-GlcNAc, intermediates from major cellular metabolic pathways including glutamine, acetyl-coA, uridine and ATP are used by the HBP (Fig. 2B), underscoring a link between UDP-GlcNAc synthesis and cell metabolic status. This link has led to the hypothesis that protein O-GlcNAcylation likely serves as a nutrient-sensitive molecular switch (18,19).

CCA is the second most common primary liver cancer after hepatocellular carcinoma (HCC), accounting for 10-15% of all primary liver cancers (20). While CCA remains relatively rare compared with other cancers, its mortality rates have been increasing worldwide since 2008-2018 (an average increase of 4% annually in the USA and Canada and 10% in Europe), especially for intrahepatic CCA (21,22). Chronic inflammation of the biliary epithelium is the key risk factor shared by all forms of CCA (20,23). Other risk factors include certain disease states affecting the flow of biliary system, such as primary sclerosing cholangitis, biliary duct cysts and hepatolithiasis (20,23). Parasitic infections, particularly with *Opisthorchis viverrini* and *Clonorchis sinensis*, which are more commonly found in Asian individuals, are also associated with increased risk of CCA. Certain metabolic conditions including diabetes, obesity, cirrhosis, alcohol consumption and smoking are also associated with CCA development (20,23).

As with other types of cancer, the therapeutic approach to CCA is multifaceted and tailored to the specific stage and characteristics of the disease. A summary of current treatment options from National Comprehensive Cancer Network (NCCN) 2023 (24) and European Society for Medical Oncology (ESMO) 2022 (25) clinical practice guidelines is provided in Table I. The advancement of molecular profiling techniques has begun to shed light on the complex genetic and molecular alterations underlying CCA and led to the identification of actionable molecular targets and their specific inhibitors (Table II) (23,26).

Despite the advancement in diagnosis and therapies, the prognosis of CCA has seen little improvement, with 7-20% 5-year overall survival rate and recurrence rate of 50-70% (20,27-29). This unsatisfactory treatment outcome thus underscores a significant gap in the understanding of CCA. The aim of the present review is thus to explore whether and how OGT and O-GlcNAcylation could be targeted for CCA treatment, using insights from other gastrointestinal (GI) tract cancers to propose potential connections.

2. Role of O-GlcNAcylation for cancer development and progression: Implications for CCA

The global increase in intracellular O-GlcNAcylation and OGT protein expression is reported in most, if not all, forms of

cancer, including those of the GI tract origin such as esophageal (30), gastric (31,32), pancreatic (33), hepatic (34,35), colorectal cancers (36,37) and CCA (38). The upregulation of OGT protein expression in cancer is consistent with the generally increased OGT mRNA expression observed in publicly accessible The Cancer Genome Atlas (TCGA) cancer samples analyzed through cBioportal (39) including CCA (Fig. 3A). The association between increased O-GlcNAcylation or OGT and poor prognosis (advanced cancer stages, metastasis or shorter survival) has been reported in GI tract cancers including esophageal (40), gastric (31), colorectal (41) and pancreatic cancer (42) and HCC (43-45). This observation is further echoed by TCGA data analyzed by Gene Expression Profiling Interactive Analysis (GEPIA) survival plot (46) demonstrating that increased OGT mRNA expression is associated with worse prognosis in esophageal carcinoma (Fig. 3B), colonic adenocarcinoma (Fig. 3C), stomach adenocarcinoma (Fig. 3D), HCC (Fig. 3E) and CCA (Fig. 3F). Moreover, elevation of OGT mRNA expression is detected in advanced stages of CCA (Fig. 3G). Upregulation of protein O-GlcNAcylation and OGT protein expression is detected in tissue from patients with CCA (38). Particularly, elevated O-GlcNAcylation is associated with non-papillary type CCA and poorer prognosis, with median survival of 401 days for OGT-positive patients (n=71) vs. 580 days for OGT-negative group (n=17).

Effect of O-GlcNAcylation on GI tract cancer growth and proliferation. A key aspect of cancer is increased proliferation. Although, to the best of our knowledge, there are no direct reports in CCA, increased OGT and O-GlcNAcylation have been linked to hyperproliferative state including increased proliferation, clonogenicity or xenograft tumor growth of most GI tract cancers including HCC (35) and pancreatic (42,47), gastric (31) and colorectal cancer (48). Notably, small interfering (si)/short hairpin (sh)RNA targeting OGT suppresses tumor growth of pancreatic (47,49), colon (50-52), gastric (31) and liver cancer (53,54). Similarly, OGT inhibition by small-molecule antagonists, such as ST045849 and OSMI-1, suppresses proliferation of GI tract cancer including HCC and colorectal cancer in both *in vitro* and *in vivo* xenograft models (35,52,55).

OGT and O-GlcNAcylation are associated with cell cycle regulation in GI tract cancer. Treatment of various cancer cell lines with small molecule inhibitors of OGT or siOGT leads to an increase in the negative regulator of cell cycle p21 both by activation of transcription and protein stabilization (56). Moreover, treatment of gastric cancer cells with siOGT inhibits proliferation and viability, accompanied by altered cell cycle distribution and decreased expression of CDK-2 and cyclin D1, and inhibits ERK 1/2 by decreasing its phosphorylation (31). Further, p27, a tumor suppressor and regulator of the cell cycle, harbors multiple O-GlcNAcylation sites (57). O-GlcNAcylation at S2 correlates with increase S10 phosphorylation, leading to an accumulation of p27 in cytoplasm and decreases p27 protein stability, favoring cell cycle progression of HCC (57). Lastly, the transcription factor FOXO3 harbors O-GlcNAcylation sites at its transactivation domain at S284 (58). Hyper-O-GlcNAcylation of wild-type FOXO3, but not the S284A O-GlcNAc deficient mutant, leads to an increase in mouse double minute 2 homolog protein

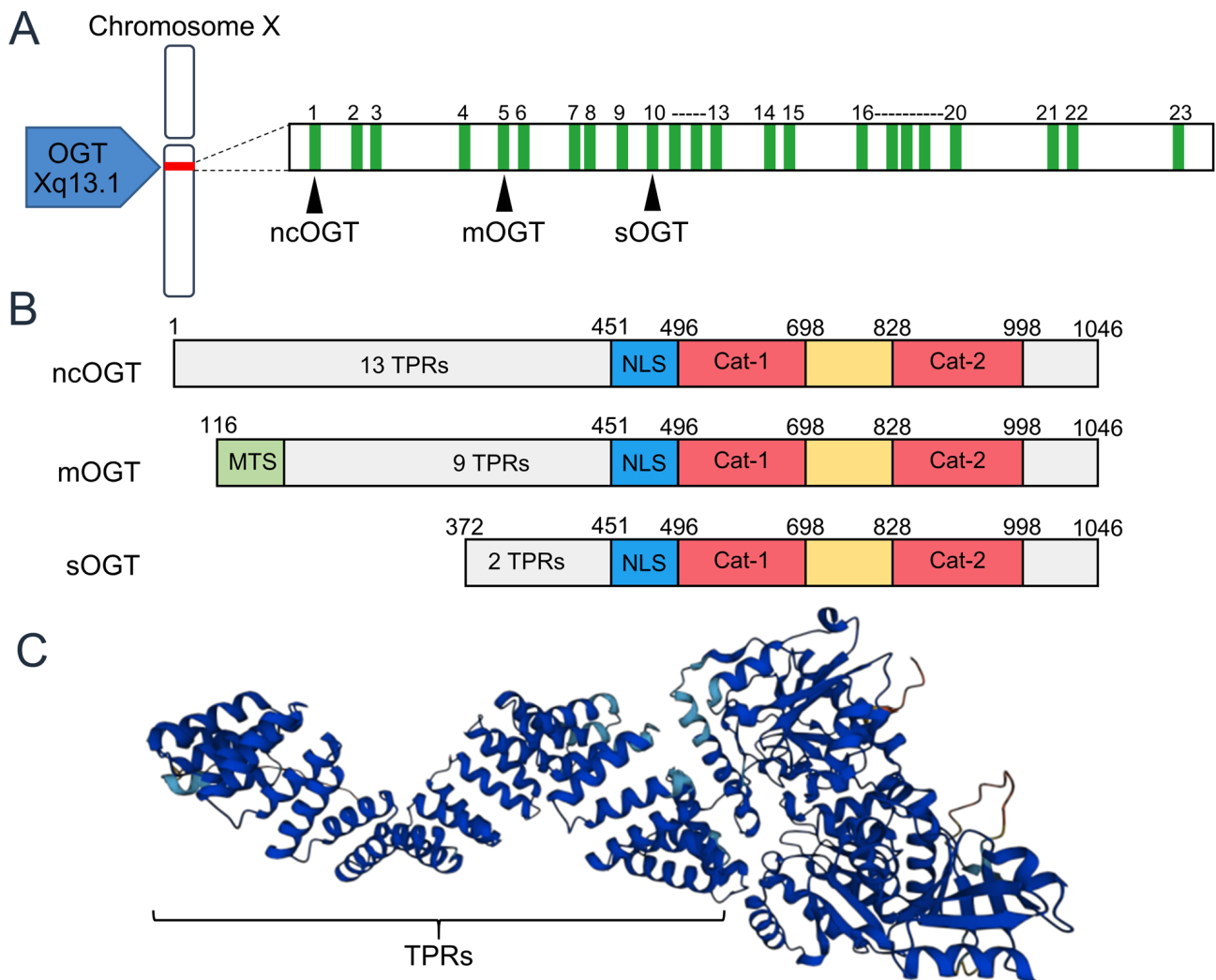


Figure 1. Schematic diagram of OGT gene and protein structure. (A) Genomic location of the human OGT gene on the X chromosome containing 23 exons (green). (B) Protein domain organization of the three OGT isoforms depicting TPR, NLS, catalytic region comprising Cat-1 and Cat-2. The mOGT isoform uniquely features a MTS at its N-terminus. Amino acid numbers marking the boundaries of each domain are also indicated. (C) 3D structure of ncOGT protein. Image retrieved from genecards.org/cgi-bin/carddisp.pl?gene=OGT. mOGT, mitochondrial O-GlcNAc transferase TPR, tetratricopeptide repeat; NLS, nuclear localization sequence; Cat, catalytic region; MTS, mitochondrial targeting sequence; nc, nucleocytoplasmic; s, short.

expression, which is accompanied by a decrease in tumor suppressors and cell cycle regulator protein p53 and p21 expression, accelerating cell proliferation (58).

The expanding knowledge regarding the role of O-GlcNAcylation in cancer has begun to elucidate a complex interplay among three major pathways frequently dysregulated in cancer: Protein O-GlcNAcylation, the pro-survival PI3K/Akt/mTOR pathway and the cancer-inhibitory AMPK pathway (59-66). Increased O-GlcNAcylation activates the PI3K/Akt/mTOR signaling pathway, leading to enhanced cancer cell proliferation and survival (59). Conversely, activation of the PI3K/Akt/mTOR pathway results in upregulation of OGT and total O-GlcNAcylation (59,60). Additionally, O-GlcNAcylation inhibits AMPK activity (61), which typically acts to suppress mTOR signaling (62). By contrast, AMPK activation downregulates OGT and total protein O-GlcNAcylation (63). Overexpression of OGT increases cell proliferation, which is accompanied by an increase in AMPK O-GlcNAcylation, reduced AMPK phosphorylation and activation of the mTOR pathway, in LoVo colorectal cancer

cells (64). This indicates the cell proliferation promotion effect of O-GlcNAcylation is potentially mediated, at least in part, through a shift in the balance between AMPK and mTOR activity; specifically AMPK O-GlcNAcylation suppresses its activity and favors mTOR pathway activation, conferring proliferative and survival benefits to cancer cells (64). Furthermore, AMPK contributes to decreased total protein O-GlcNAcylation via the AMPK-mediated phosphorylation of GFAT1 at S243, which suppresses GFAT activity (65,66). This dynamic suggests a positive reciprocal association between O-GlcNAcylation and the PI3K/Akt/mTOR pathway, while the interaction between O-GlcNAcylation and the AMPK pathway may function as a negative feedback mechanism.

O-GlcNAcylation promotes CCA metastasis. The direct link between OGT and O-GlcNAcylation to CCA metastasis has been revealed by Phoomak *et al* (67): Transwell assay of CCA cell lines treated with siRNA targeting OGT demonstrated a marked decrease in invasion and migration. O-GlcNAc may regulate CCA metastasis through a modification of NF- κ B,

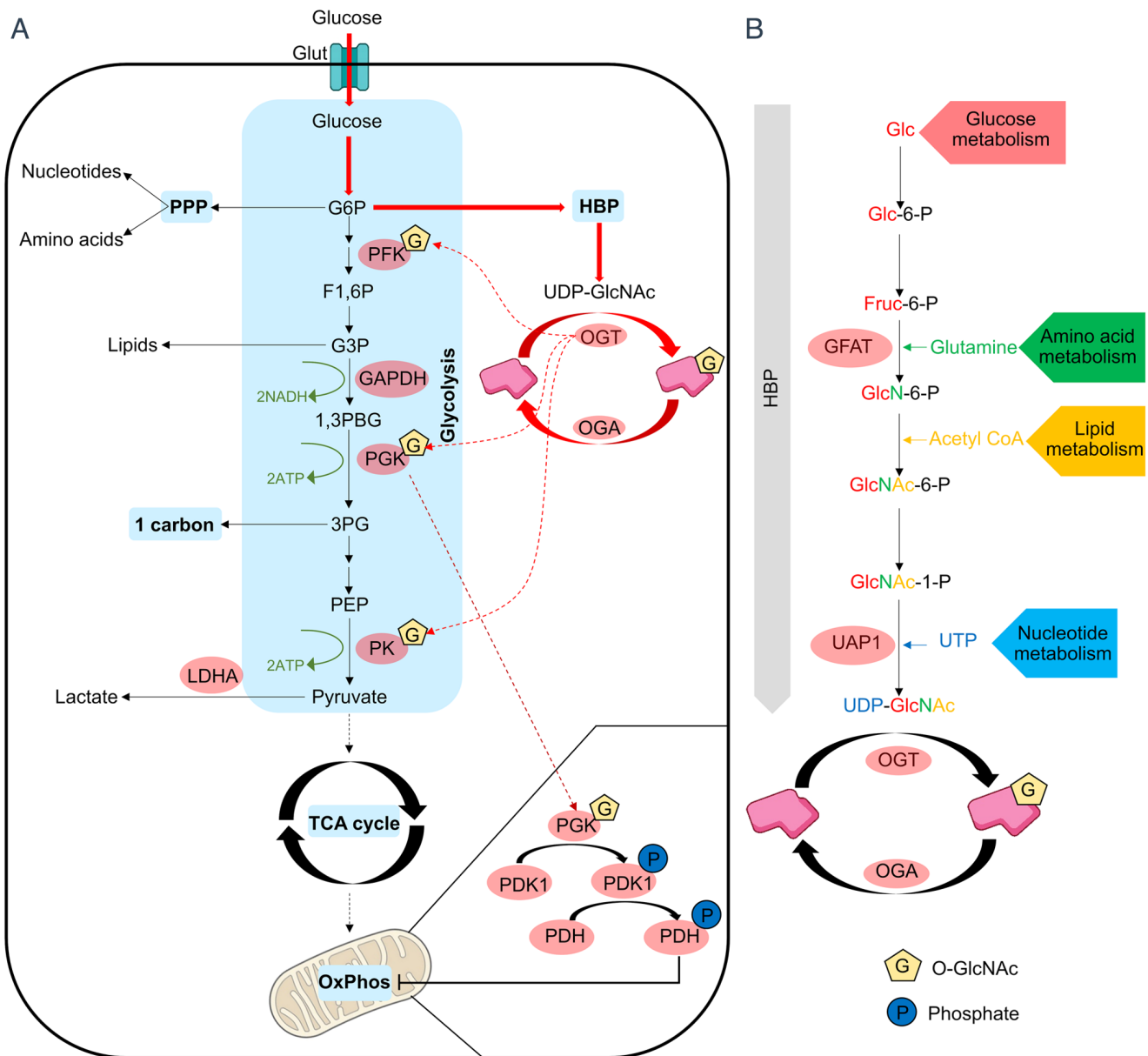


Figure 2. O-GlcNAcylation pathway and its association with glucose metabolism. (A) UDP-GlcNAc, the GlcNAc donor molecule, is synthesized via the HBP, a metabolic branch stemming from glycolysis. Glycolysis is associated with other metabolic pathways, including the TCA cycle, OxPhos, PPP and one-carbon cycle. (B) HBP pathway integrates glucose, amino acid, lipid and nucleotide metabolism in the synthesis of the donor molecule UDP-GlcNAc. Figure constructed using BioArt (bioart.niaid.nih.gov/). UDP-GlcNAc, uridine diphosphate N-acetylglucosamine; HBP, hexosamine biosynthesis pathway; TCA, tricarboxylic acid cycle; OxPhos, oxidative phosphorylation; PPP, pentose phosphate pathway; OGT, O-GlcNAc transferase; OGA, O-GlcNAcase; PFK, phosphofructokinase; G6P, glucose-6-phosphate; F1,6P, fructose 1,6-bisphosphate; G3P, glyceraldehyde-3-phosphate; 1,3PBPG, 1,3-bisphosphoglycerate; 3PG, 3-phosphoglycerate; PEP, phosphoenolpyruvate; PGK, phosphoglycerate kinase; PK, pyruvate kinase; LDHA, lactate dehydrogenase A; PDH, pyruvate dehydrogenase; GFAT, glutamine fructose-6-phosphate amidotransferase; Fruc, fructose; UAP, UDP-N-acetylglucosamine pyrophosphorylase 1; Glut, glucose transporter; UTP, uridine triphosphate.

a cancer-relevant transcription factor and a well-established regulator metastasis (67,68). NF- κ B is a substrate of OGT and its modification is key for nuclear translocation and subsequent activation of matrix MMPs (67). Additionally, that high glucose (25.0 vs. 5.6 mM in conventional cell culture media) elicits a similar effect in CCA cell lines, accompanied by upregulation of O-GlcNAcylated proteins, vimentin, hexokinase, GFAT and OGT (68). Moreover, treatment with 6-diazo-5-oxo-L-norleucine (DON), an inhibitor of GFAT, could reverse this effect as well as decrease migration (68). The association between O-GlcNAcylation and OGT and cancer metastasis has also

been detected in other GI tract cancer, including colorectal cancer (69) and HCC (35).

Interplay between O-GlcNAcylation and cancer metabolic reprogramming. To meet the increased demand posed by hyperactive proliferation, cancer cells often rewire key metabolic processes (cancer metabolic reprogramming). This adaptive mechanism enables cancer cells to modify their metabolism, allowing them to efficiently utilize nutrients such as glucose, lipids and amino acids to support their rapid proliferation and survival.

Table I. Pharmacological treatment options for cholangiocarcinoma modified from National Comprehensive Cancer Network 2023 and European Society for Medical Oncology 2022 clinical practice guidelines and emerging actionable targets with corresponding inhibitors.

Stage of the disease	Treatment options	(Refs.)
Early	Surgical resection and adjuvant therapy with capecitabine	(25)
Locally advanced	Cisplatin + gemcitabine ± durvalumab	(25)
Advanced or metastatic	Cisplatin + gemcitabine ± durvalumab; 5-FU + folinic acid + oxaliplatin or irinotecan; capecitabine + oxaliplatin; gemcitabine + albumin-bound paclitaxel (in the presence or absence of cisplatin), capecitabine or oxaliplatin; FGFR2 fusion liposomal irinotecan + 5-FU + folinic acid; 5-FU ± irinotecan; regorafenib;	(24,25)
5-FU, 5-fluorouracil		

Table II. Actionable targets for cholangiocarcinoma

Actionable targets	Drugs
IDH1	Ivosidenib
FGFR2 fusion	Pemigatinib, futibatinib, infigratinib
EGFR and HER	Cetuximab, panitumumab, trastuzumab, fam-trastuzumab deruxtecan-nxki, pertuzumab, lapatinib
BRAF V600E	Dabrafenib + trametinib
MSI-H/dMMR	Pembrolizumab, dostarlimab-gxly
TMB-H	Nivolumab + ipilimumab, pembrolizumab
NTRK fusion	Larotrectinib, entrectinib
RET fusion	Pralsetinib, selpercatinib; nivolumab; lenvatinib + pembrolizumab
PI3K	Copanlisib, buparlisib, pilaralisib, idelalisib
AKT	Perifosine, ipatasertib, MK-2206, capivasertib, GSK690693
IL6 signaling	Tocilizumab
VEGF signaling	Bevacizumab, ramucirumab, sorafenib, sunitinib, cediranib
TGFβ signaling	Galunisertib
SRC	Saracatinib, dasatinib, bosutinib
JAK 1/2	Ruxolitinib, AZD1480, tofacitinib, fedratinib
STAT3	OPB-31121
ERK 1/2	SCH772984, VTX11e
WNT	Ipafricept, CWP232291, PRI-724, LGK974
MET/ROS/ALK	Crizotinib
PARP1/2	Veliparib

IDH, isocitrate dehydrogenase; FGFR, fibroblast growth factor receptor; EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor; BRAF, B-Raf proto-oncogene, serine/threonine kinase; MSI-H, microsatellite instability-high; dMMR, deficient mismatch repair; TMB-H, tumor mutational burden-high; NTRK, neurotrophic tyrosine receptor kinase; VEGF, vascular endothelial growth factor; TGF, transforming growth factor; SRC, proto-oncogene tyrosine-protein kinase Src; JAK, janus kinase; ROS, ROS proto-oncogene 1, receptor tyrosine kinase; ALK, anaplastic lymphoma kinase; PARP, poly(ADP-ribose)transferase.

O-GlcNAcylation regulates key metabolic pathways

O-GlcNAcylation as a driver of the Warburg effect: enhancing glycolysis while suppressing the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OxPhos). A hallmark of cancer metabolic reprogramming is the shift towards aerobic glycolysis, accompanied by the decreased reliance on the TCA cycle and OxPhos (70). Known as the Warburg effect, this

phenomenon describes how cancer cells preferentially convert glucose to lactate in the presence of sufficient oxygen (70). Aerobic glycolysis enables cancer cells to efficiently produce ATP, maintain redox homeostasis, regenerate electron carriers such as NAD⁺ and generate biomass, including lipids, nucleotides and amino acids (70). By adopting this metabolic strategy, cancer cells meet their energy needs while

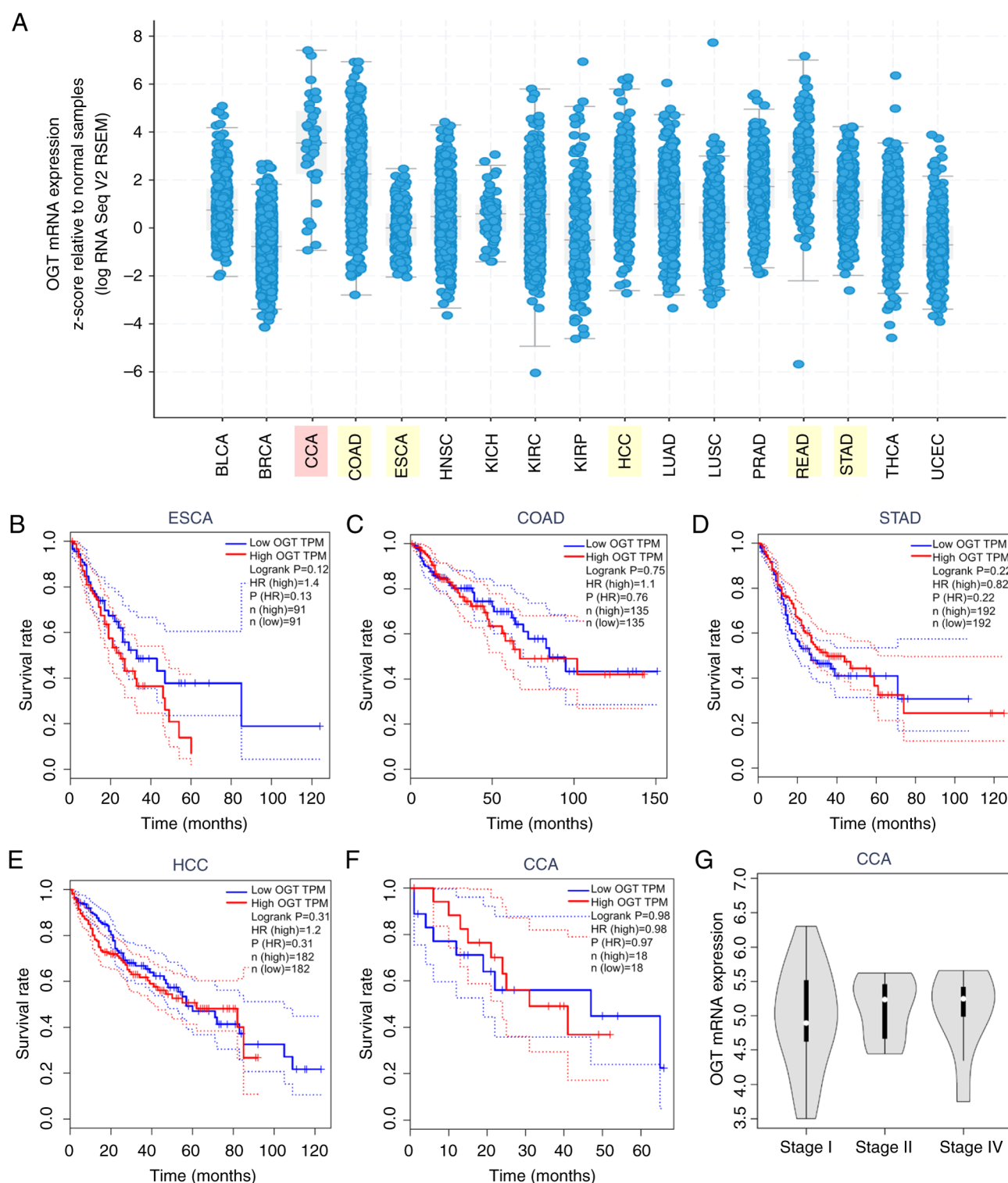


Figure 3. OGT mRNA expression status and association with poor prognosis in certain GI tract cancers in TCGA. (A) OGT mRNA expression relative to normal samples in various cancer types. GI tract cancer and CCAs are highlighted in yellow and red, respectively. Association between OGT mRNA expression and prognosis of (B) ESCA, (C) COAD, (D) STAD, (E) HCC and (F) CCA. (G) Association between OGT mRNA expression and tumor stage in CCA from TCGA data analyzed with Gene Expression Profiling Interactive analysis stage plot. OGT, O-GlcNAc transferase; TPM, transcripts per million; RSEM, release sequence expression measurer; GI, gastrointestinal; TCGA, The Cancer Genome Atlas; CCA, cholangiocarcinoma; ESCA, esophageal carcinoma; COAD, colon adenocarcinoma; STAD, stomach adenocarcinoma; HCC, hepatocellular carcinoma.

ensuring a continuous supply of building blocks key for rapid proliferation and survival (70).

Accumulated evidence supports the role of O-GlcNAcylation as a positive regulator of glycolysis (51,71-73). Itkonen *et al* (71) demonstrated that inhibiting OGT decreases the expression of

c-MYC and CDK1, leading to growth suppression in prostate cancer. OGT inhibition also decreases glucose consumption and lactate production, indicating a suppression of glycolysis (71). Additionally, phosphoglycerate kinase 1 (PGK1), the first ATP-generating enzyme in glycolysis (Fig. 2A),

undergoes O-GlcNAcylation at T255, which enhances its enzymatic activity and promotes glycolysis (72). This also facilitates the translocation of PGK1 to the mitochondria, where it serves as a kinase to phosphorylate and activate pyruvate dehydrogenase kinase 1 (PDK1, Fig. 2A). Activated PDK1 phosphorylates and inhibits pyruvate dehydrogenase (PDH, Fig. 2A), thereby suppressing OxPhos. Elevated PGK1 O-GlcNAcylation has been observed in human colon cancer, and disruption of O-GlcNAcylation at T255 suppresses PGK1 oncogenic activity (72), underscoring its role in cancer metabolism and progression. c-Myc has also been implicated in this axis. Mechanistically, O-GlcNAcylation of c-Myc at S415 enhances c-Myc stability, increasing its transcriptional activity and leading to the upregulation of PDK2 (51). PDK2 phosphorylates and inhibits PDH, thereby suppressing PDH activity and limiting the TCA cycle (51). Notably, elevated c-Myc S415 glycosylation is associated with increased PDK2 expression in colorectal cancer tissue (51). Taken together, these data indicate that O-GlcNAcylation suppresses the TCA cycle and OxPhos, redirecting glucose flux toward glycolysis and other branched metabolic pathways including HBP via the OGT-PGK1/c-Myc-PDK1/2-PDH axis.

Pyruvate kinase M2 (PKM2), an isoform of the PK enzyme (Fig. 2A), catalyzes the final step of glycolysis by converting phosphoenolpyruvate to pyruvate. PKM2 exists in dynamic oligomeric states, serving either as a catalytically active tetramer or as less active dimers and monomers. In cancer cells, PKM2 predominantly adopts low-activity dimeric or monomeric forms, thereby limiting pyruvate production and diverting upstream glycolytic intermediates toward biosynthetic pathways rather than OxPhos. Under conditions of high glucose, PKM2 undergoes O-GlcNAcylation, which decreases its tetramerization and diminishes its enzymatic activity (73).

Isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) are among the most frequently mutated metabolic enzymes in human cancer. These gain-of-function mutations result in an aberrant enzymatic activity that converts α -ketoglutarate to the oncometabolite R-2-hydroxyglutarate (R-2HG) (74). Accumulation of R-2HG leads to competitive inhibition of a range of α -ketoglutarate-dependent dioxygenases, thereby disrupting key cell processes such as epigenetic regulation, DNA repair and cellular metabolism (74). Among dioxygenase targets are the Jumonji C domain-containing histone demethylases (KDMs) and the ten-eleven translocation (TET) family of DNA demethylases (74). Inhibition of KDMs by mutant IDH1 leads to global increases in histone methylation at key residues such as H3K4, H3K9 and H3K27, contributing to transcriptional dysregulation and impaired DNA damage response (74). Similarly, TET enzyme inhibition results in decreased levels of 5-hydroxymethylcytosine, altering the DNA methylation landscape and gene expression (74). Notably, IDH mutations are particularly enriched in intrahepatic CCA, where they represent a distinct molecular subtype with specific therapeutic vulnerabilities, particularly to IDH inhibitors (74).

The upregulation of IDH2 has been observed in colorectal cancer tissue and is associated with poor patient survival (75). Overexpression of IDH2 not only promotes colorectal cancer growth but also enhances glycolytic activity. Moreover, treatment of colorectal cancer cells with α -ketoglutarate, a product of IDH2, activates NF- κ B signaling, which in

turn upregulates glucose transporter 1 (GLUT1) expression and promotes glucose uptake (75). Increased glucose flux, associated to heightened HBP activity, elevates intracellular O-GlcNAcylation. Consequently, the upregulation of IDH2 drives O-GlcNAcylation via the NF- κ B-GLUT1 axis. IDH2 is O-GlcNAcyated, a modification that is associated with enhanced IDH2 protein stability, suggesting that O-GlcNAcylation promotes IDH2 activity, modulating its turnover (75). This interplay creates a feed-forward loop, where IDH2 and O-GlcNAcylation cooperatively reprogram metabolism to support colorectal cancer progression and growth.

O-GlcNAcylation positively regulates pentose phosphate pathway (PPP). PPP is a key metabolic route that supports rapid cell proliferation by supplying macromolecule precursors and redox metabolites. Upregulation of the PPP has been observed in numerous types of cancer including esophageal, gastric, colonic, lung and breast cancer and potentially CCA (76). Notably, O-GlcNAcylation has been identified as a positive regulator of the PPP through multiple mechanisms. Phosphofructokinase 1 (PFK1), an enzyme in glycolysis (Fig. 2A), undergoes O-GlcNAcylation at S529 under hypoxic condition (77). This glycosylation suppresses PFK1 activity, thereby redirecting glucose through parallel metabolic pathways such as PPP, conferring proliferative advantage for lung cancer cells (77). Disruption of PFK1 O-GlcNAcylation at S529 significantly decreases cancer growth *in vitro* and *in vivo* (77). Additionally, glucose-6-phosphate dehydrogenase (G6PD), the rate-limiting enzyme of the PPP, is O-GlcNAcyated at S86 under hypoxia, which enhances its activity and increases glucose flux via the PPP (76). Depleting G6PD O-GlcNAcylation via site-directed mutagenesis similarly suppresses lung cancer growth *in vitro* and *in vivo* (76). Although these regulatory mechanisms of O-GlcNAcylation on the PPP have been characterized in lung cancer (76), similar mechanisms may operate in other cancer types, given the fundamental role of the PPP in metabolism across diverse cell types.

O-GlcNAcylation positively regulates de novo lipid synthesis. In addition to their heightened glucose requirements, cancer cells exhibit an increased demand for lipid synthesis and uptake to support membrane biogenesis, energy production and signaling (78,79). Many cancer cells reprogram their metabolism to activate *de novo* lipogenesis, decreasing their dependence on external lipid sources (78,79). Notably, O-GlcNAcylation has been implicated in this metabolic rewiring, serving a key role in driving lipid synthesis and metabolic adaptation in cancer (80,81).

O-GlcNAcylation modulates lipid metabolism in cancer cells through its effects on the transcription factor sterol regulatory element-binding protein 1 (SREBP-1), a master regulator of lipid metabolism (80). In breast cancer, OGT influences SREBP-1 expression by modulating the activity of AMP-activated protein kinase (AMPK), a negative regulator of SREBP-1 (80). Depletion of OGT via shRNA leads to lipogenic defects, but overexpression of SREBP-1 rescues these defects and restores tumor growth *in vitro* and *in vivo* (80). This highlights the key role of SREBP-1 in OGT-mediated regulation of lipid metabolism, a critical process for cancer progression. Additionally, O-GlcNAcylation of serine/arginine-rich protein

kinase 2 (SRPK2) at its nuclear localization signal promotes its translocation to the nucleus (81). Once localized in the nucleus, SRPK2 phosphorylates serine/arginine-rich proteins and facilitates pre-mRNA splicing of key lipogenic genes such as fatty acid synthase (FASN), farnesyl-diphosphate farnesyl-transferase 1, ATP citrate lyase and mevalonate diphosphate decarboxylase (81).

Metabolic association between O-GlcNAcylation and c-Myc in cancer. Upregulation of the oncogene c-Myc is observed in at least 40% of tumors (82). As a transcription factor, c-Myc regulates genes involved in key cellular processes that drive cancer transformation and progression, including proliferation, differentiation, cell cycle control, metabolism and apoptosis (82,83). Moreover, c-Myc serves a critical role in cancer metabolic reprogramming by controlling genes associated with multiple metabolic pathways. Morrish *et al* (84) demonstrated that c-Myc is not only key for glycolysis but also enhances the activity of auxiliary metabolic pathways necessary for macromolecule synthesis, such as the one-carbon pathway and the PPP. O-GlcNAcylation positively regulates c-Myc by enhancing its protein stability (51,85,86), eventually amplifying its transcriptional activity. c-Myc expression is also associated with increased global O-GlcNAcylation (60,84), creating a feed-forward loop that reinforces metabolic reprogramming. In support of this interplay, inhibition of HBP with the small-molecule GFAT inhibitor DON suppresses proliferation of Myc-expressing cells (84). Together, these findings underscore the cooperative association between O-GlcNAcylation and c-Myc in orchestrating cancer metabolic reprogramming, enabling cancer growth and progression.

Effects of cell metabolism on protein O-GlcNAcylation. OGT and intracellular O-GlcNAcylation are controlled by cell glucose metabolism in GI tract cancer. High glucose levels are a contributing factor for cancer progression. In HCC, advanced glycosylation end product-specific receptor (AGER) has been shown to activate the HBP, resulting in an overall increase in O-GlcNAcylation levels (54). This elevated O-GlcNAcylation enhances the O-GlcNAcylation of the proto-oncoprotein c-Jun at S73, which stabilizes c-Jun and promotes its activity (54). Moreover, c-Jun reciprocally enhances AGER transcription, establishing a positive feedback loop that may accelerate cancer growth under conditions of high glucose availability (54). AGER overexpression has been detected in ~25% of peripheral-type intrahepatic CCA cases and is associated with poor overall survival (87). Additionally, high expression of S100A6, a ligand of AGER, has been observed in intrahepatic CCA and is associated with lymph node metastasis (88). Mechanistically, S100A6 activates AGER signaling and promotes angiogenesis both *in vitro* and *in vivo* via NF- κ B-mediated upregulation of vascular endothelial growth factor (VEGF)-D, which is counteracted by inhibition of either AGER or NF- κ B signaling (88). These findings suggest that AGER is a driver of pathogenesis and aggressive phenotype of a specific subset of CCA, which is modulated by O-GlcNAcylation.

Additionally, glucose promotes the O-GlcNAcylation of casein kinase 2, which inhibits the phosphorylation of the protein constitutive photomorphogenesis (COP)9 signalosome and prevents its binding to the CUL4-RING E3 ubiquitin ligase

complex (CRL4). This interaction allows CRL4 to associate with COP1, resulting in the formation of an active CRL4-COP1 E3 ligase complex that targets the tumor suppressor protein p53 for degradation (89). β -catenin, the key signal transducer in the Wnt signaling pathway, is commonly upregulated in various cancers including HCC, colorectal, breast and prostate cancer and osteosarcoma (90). β -catenin upregulation leads to an upregulation of UDP-N-acetylglucosamine pyrophosphorylase 1 (UAP1), the final enzyme in the HBP pathway. UAP1 catalyzes the conversion of UTP and glucosamine 1-phosphate into UDP-GlcNAc (Fig. 2B), the primary donor molecule for O-GlcNAcylation. The upregulation of UAP1, which is mediated by increased protein stability, increases glucose flux and global O-GlcNAcylation levels, promoting the growth of HCC (44). Conversely, O-GlcNAcylation directly increases the protein stability of β -catenin, creating a feed-forward mechanism that further amplifies β -catenin signaling (44).

Additionally, OGT and O-GlcNAcylation are regulated by lipid metabolism. FASN, a key enzyme in the *de novo* lipid synthesis pathway, is upregulated in numerous types of cancer, including colorectal cancer, and contributes to tumor progression (52). Drury *et al* (52) demonstrated that the oncogenic effects of FASN are mediated through upregulation of glutamine-fructose-6-phosphate transaminase 1 (GFPT1) and OGT (52). This corroborates research by Raab *et al* (91), which indicated that inhibiting FASN with a small-molecule inhibitor reduces OGT expression, overall O-GlcNAcylation and mTOR activation. Furthermore, FASN expression is influenced by both O-GlcNAcylation and mTOR signaling pathways (91). Collectively, these findings highlight the interaction between FASN and O-GlcNAcylation in a feed-forward manner that promotes tumorigenesis and cancer progression. Further, acyl-CoA ligase 4 (ACSL4) is upregulated and associated with poor prognosis in HCC (45). ACSL4 collaborates with O-GlcNAc to rewire glucose metabolism, facilitating cancer growth. Mechanistically, the upregulation of ACSL4 is associated with GLUT1 stabilization, leading to increased glucose flux and elevated global O-GlcNAcylation in cancer cells (45). Conversely, ACSL4 is modified through O-GlcNAcylation, which enhances its protein stability. This positive reciprocal association between ACSL4 and O-GlcNAcylation demonstrates the complex interplay that drives metabolic reprogramming in cancer cells, promoting tumor growth and progression.

Collectively, the crosstalk between O-GlcNAcylation and cellular metabolism underscores the key role of OGT and O-GlcNAcylation as central facilitators of cancer metabolic reprogramming. This highlights a critical mechanism by which nutrient availability modulates oncogenic signaling pathways, contributing to the aggressive progression of GI tract cancer, including potentially CCA. Exploring these dynamic interconnections may unveil novel therapeutic strategies for targeting cancer metabolism.

O-GlcNAcylation: A positive regulator of angiogenesis. The induction of angiogenesis during tumorigenesis is a well-established hallmark of cancer (70). Beyond supplying oxygen and nutrients to support tumor growth, angiogenesis facilitates cancer cell invasion into surrounding tissue and promotes metastasis to distant organs (70). Although direct reports of the

involvement of O-GlcNAcylation in angiogenesis of CCA are limited, studies on the regulation of OGT mRNA by circular RNAs and microRNAs in other types of cancer indicate that OGT, and potentially downstream O-GlcNAcylation, plays a critical role in promoting tumor angiogenesis (92,93).

Several pro-angiogenic factors, particularly VEGFs, drive endothelial cell proliferation and differentiation (70). To sustain angiogenesis, tumors require continuous remodeling of the stroma, a process that depends on MMPs, which degrade the extracellular matrix (94). Lynch *et al* (95) demonstrated that decreasing hyper-O-GlcNAcylation in PC-3ML prostate cancer cells via OGT knockdown leads to decreased expression of MMP-2, MMP-9 and VEGF, and impaired *in vitro* angiogenesis. This effect was mediated by regulation of the oncogenic transcription factor FOXM1, a known driver of invasion and angiogenesis, whose protein stability was maintained by OGT (95). Similarly, the role of OGT and O-GlcNAcylation in upregulating MMPs and VEGF has been reported in HCC (96) and breast cancer (92), supporting the pro-angiogenic function of O-GlcNAcylation.

Beyond transcriptional control, O-GlcNAcylation enhances angiogenesis by modulating protein translation. For example, in HCC cells, O-GlcNAcylation of ribosomal receptor for activated C-kinase 1 (RACK1), a key player in translation process, at Ser122 stabilizes the protein, enhancing its activity (97). Mutation of this site to prevent O-GlcNAcylation suppresses tumor growth, angiogenesis and metastasis both *in vitro* and *in vivo* (97). Finally, HCC patient sample analyses confirmed that elevated RACK1 O-GlcNAcylation is associated with tumor progression and angiogenesis (97).

While disrupting OGT or O-GlcNAcylation in tumor cells may suppress angiogenesis, the opposite effect has been observed in normal endothelial cells (65,98). Zibrova *et al* (65) reported that inhibition of GFAT, the rate-limiting enzyme of the HBP pathway, decreases O-GlcNAc levels but paradoxically enhances angiogenesis. This is further supported by an earlier finding by Luo *et al* (98), which showed that elevating O-GlcNAcylation levels inhibits angiogenesis in endothelial cells. These opposing outcomes highlight a possible context-dependent role of O-GlcNAcylation in physiological vs. oncological angiogenesis. Li *et al* (99) investigated the tumor-endothelial cell interaction within the tumor microenvironment (TME): In bladder cancer, tumor cells secrete small extracellular vesicles containing GFAT1, which are taken up by endothelial cells, leading to increased HBP flux and O-GlcNAcylation. This modifies seryl-tRNA synthetase (SerRS) at Ser101, promoting its degradation. As SerRS acts as a negative regulator of VEGF transcription, its downregulation leads to elevated VEGF expression and enhanced angiogenesis (99). Together, these findings underscore the complex and context-specific roles of O-GlcNAcylation in angiogenesis, acting as a tumor-promoting factor in cancer cells, while its effects in normal endothelial cells vary depending on microenvironmental cues and intercellular communication.

O-GlcNAcylation and programmed cell death (PCD). PCD is central to cancer biology, serving both as a tumor-suppressive mechanism and as a process cancer cells manipulate to support survival and therapy resistance, making death resistance a hallmark of cancer (100). Classical PCD pathways

include apoptosis, autophagy and necroptosis, with more recently described modalities such as ferroptosis and pyroptosis also gaining attention (101-103). Non-canonical forms such as anoikis, parthanatos, entosis and oxeiptosis add complexity. In CCA, PCD not only contributes to pathogenesis but also represents a potential therapeutic target (102,103).

O-GlcNAcylation as a key anti-apoptotic mechanism. Apoptosis is a form of PCD involving distinct morphological and molecular changes, driven by intrinsic (mitochondrial) or extrinsic (death receptor-mediated) pathways that converge on executioner caspases (101). Although direct evidence in CCA is limited, hyper-O-GlcNAcylation broadly promotes apoptosis resistance in cancer (49,104-111). Mechanistically, OGT inhibition using OSMI-1 induces reactive oxygen species (ROS)-mediated endoplasmic reticulum (ER) stress, activating C/EBP homologous protein (CHOP)-death receptor 5 and JNK signaling, decreasing Bcl2 levels, promoting cytochrome c release and triggering apoptosis (112). Similar pro-apoptotic outcomes following OGT depletion occur in breast cancer via disrupted metabolism, increased ER stress and induction of pro-apoptotic Bcl2-family proteins Bcl-2 interacting mediator of cell death, p53-upregulated modulator of apoptosis (Puma) and phorbol-12-myristate-13-acetate-induced protein 1 (Noxa), regulated by hypoxia-inducible factor-1 α (HIF-1 α) and CHOP signaling which are positively regulated by O-GlcNAcylation (113).

O-GlcNAcylation exerts anti-apoptotic effect by supporting oncogenic transcriptional programs. In pancreatic ductal adenocarcinoma, hyper-O-GlcNAcylation sustains NF- κ B activity via modification of p65 and upstream inhibitor of κ B kinases IKK α / β (46). Decreasing O-GlcNAcylation impairs NF- κ B signaling and apoptosis resistance (49). In HCC, O-GlcNAcylation stabilizes β -catenin, which upregulates O-GlcNAcylation levels through UAP1, forming a reciprocal loop that enhances proliferation and apoptosis resistance (44).

Additionally, in colon cancer, O-GlcNAcylation modulates senescence to evade cell death. In p53-proficient colon cancer cells, therapy-induced senescence is accompanied by decreased expression of GFAT, OGT and OGA, leading to decreased O-GlcNAcylation (107). Preventing this adaptive decrease in O-GlcNAcylation shifts cell fate from senescence to apoptosis via enhanced DNA damage, as shown in cell lines and patient-derived tumoroids (114).

Dual role of O-GlcNAcylation in autophagy. Autophagy maintains cell homeostasis by degrading damaged organelles and proteins via autophagosomes that fuse with lysosomes (101). While initially tumor-suppressive, autophagy supports cancer cell survival under stress in established tumors (101). Initiation involves Unc-51-like kinase 1 (ULK1) complex activation, phagophore formation, recruitment of autophagy-related (ATG) proteins and lipidation of LC3 (ATG8) to form LC3-II (101). As the phagophore expands, it engulfs cytoplasmic constituents, such as damaged organelles or protein aggregates, sealing to form a double-membraned autophagosome (101). Autophagosomes fuse with lysosomes to degrade their contents (101). Autophagy is regulated by nutrient sensing (mTOR and AMPK signaling) (101).

The precise role of O-GlcNAcylation in autophagy remains controversial and appears broadly context-dependent. Several studies report a pro-autophagic role. In glioblastoma, cancerous and non-cancerous colon cells and Alzheimer's disease *in vitro* and *in vivo* mouse models, enhancing O-GlcNAcylation promotes autophagy (115-117). Mechanistically, ATG4B and ULK1 are directly O-GlcNAcylated, increasing their activity and stability, respectively, under metabolic stress or human papillomavirus infection (118,119). Conversely, other studies indicate that O-GlcNAcylation inhibits autophagy (108,120-123). In several cancer and inflammatory disease models, O-GlcNAcylation of synaptosome associated protein 29 disrupts soluble N-ethylmaleimide-sensitive factor activating protein receptor (SNARE) complex formation, impairing autophagosome-lysosome fusion and limiting autophagic flux (108,120-123). Despite these conflicting findings, both autophagy and O-GlcNAcylation act as adaptive, pro-survival mechanisms in cancer under various stress (124) or therapeutic interventions (108,115,123). Understanding their crosstalk may reveal strategies to overcome therapy resistance.

O-GlcNAcylation as a regulator of ferroptosis. Ferroptosis is a distinct iron-dependent PCD characterized by lipid peroxidation and oxidative damage. It is regulated by antioxidant systems, iron metabolism and lipid peroxidation pathways (125). Emerging evidence links O-GlcNAcylation to ferroptosis resistance in cancer (15,125,126). One mechanism involves enhanced glutathione (GSH) synthesis. In HCC, O-GlcNAcylation of the cysteine transporter SLC7A11 at Ser26 increases cystine uptake (126). As cysteine is a key precursor for GSH synthesis, O-GlcNAcylation increases GSH levels and protects against ferroptosis (126). Additionally, O-GlcNAcylation stabilizes transcription factors that promote ferroptosis resistance. In nasopharyngeal carcinoma, O-GlcNAcylation of the transcription factor HOXA9 increases its stability and suppresses Sirtuin 6, decreasing iron accumulation and lipid peroxidation (127). Similarly, in neuroblastoma, OGT modifies and stabilizes the transcription factor FOXO1, promoting expression of metabolic and ferroptosis-protective genes such as asparagine synthetase (ASNS), glutamate pyruvate transaminase 2, cystathionine β -synthase and ferritin heavy chain 1 (FTH1) (128).

In clear cell renal cell carcinoma, OGT stabilizes HIF-2 α , which promotes accumulation of polyunsaturated lipids, increasing sensitivity to ferroptosis (129). While OGT upregulation does not directly cause cell death, it sensitizes cells to ferroptosis inducer erastin, suggesting a context-dependent role (129). This highlights the context-dependent nature of O-GlcNAcylation-ferroptosis interplay.

While the precise role of O-GlcNAcylation in ferroptosis is not yet fully understood, there is an association between O-GlcNAcylation and metabolic status and its intricate crosstalk with key redox homeostasis pathways. Further unraveling of this complex association may enable the development of innovative, cancer-specific treatment approaches simultaneously targeting metabolic vulnerabilities and cell death pathways.

O-GlcNAcylation in necroptosis. Necroptosis is a lytic, pro-inflammatory PCD activated under caspase inhibition and mediated by receptor-interacting protein kinase (RIPK)1

and RIPK3, and the executioner molecule mixed lineage kinase domain-like pseudokinase (MLKL), which disrupts membrane integrity upon phosphorylation (101). While it may compensate for defective apoptosis, its immunogenic effects both suppress and promote tumor growth (101). Evidence on O-GlcNAcylation in necroptosis is limited but suggests a suppressive role (130,131). O-GlcNAcylation of RIPK3 at Thr467 inhibits its dimerization and downstream signaling (130). In a mouse liver fibrosis model, OGT loss increases RIPK3 and MLKL expression and stability, promoting hepatocyte necroptosis (131). These findings highlight OGT as a potential modulator of necroptosis through post-translational control of key effectors.

Role of O-GlcNAcylation in CCA-associated inflammation and immunity. The tumorigenesis and progression of CCA is associated with chronic inflammation. While the etiological landscape of CCA is heterogeneous, encompassing conditions such as primary sclerosing cholangitis, liver fluke infection and hepatolithiasis, most of these risk factors converge upon persistent biliary inflammation (132-134). This prolonged inflammatory insult induces a cycle of epithelial injury and regeneration, creating a pro-neoplastic microenvironment. Immune cell infiltration, particularly by macrophages, amplifies the inflammatory response via the release of key mediators, including IL-6, IL-33, TNF- α , COX-2 and Wnt ligands. These mediators facilitate uncontrolled proliferation, inhibit apoptotic mechanisms and induce DNA damage, thereby promoting genomic instability and epigenetic reprogramming, which collectively drive carcinogenesis (132,133).

Key oncogenic signaling cascades such as NF- κ B, STAT3, activator protein 1 (AP-1)/JNK and Hedgehog (Hh), are typically activated within this inflammatory milieu, orchestrating a transcriptional program that promotes cell survival, proliferation and differentiation (132-134). Although the broader role of O-GlcNAcylation in modulating inflammation and tumor immunity is recognized (135), its direct involvement in CCA-associated inflammation remains largely unclear.

O-GlcNAcylation regulates key transcription factors mediating inflammatory signaling. Cancer-associated inflammation involves widespread dysregulation of intracellular signaling pathways. Transcription factors such as NF- κ B, STAT1/3, AP-1 and Hh-/glioma-associated oncogene homolog (GLI) are central to this process, modulating the inflammatory milieu through cytokines, chemokines and immune cell recruitment (135). O-GlcNAcylation serves a crucial role in modulating the activity of these transcription factors, linking metabolic flux with inflammatory signaling (135).

NF- κ B signaling. NF- κ B is a key regulator of inflammation and immune responses (135). The canonical NF- κ B complex includes five subunits: RelA (p65), RelB, c-Rel, p50/p105 (NF- κ B1), and p52/p100 (NF- κ B2) (135). Under physiological conditions, NF- κ B is sequestered in the cytoplasm by I κ Bs (135). Activation occurs via phosphorylation and proteasomal degradation of I κ Bs by the IKK complex, allowing NF- κ B to translocate into the nucleus and initiate transcription (135).

In CCA, O-GlcNAcylation of NF- κ B subunits, particularly p65 and c-Rel, enhances their nuclear translocation and transcriptional activity, promoting the expression of pro-tumorigenic genes such as MMPs (67). O-GlcNAcylation decreases binding affinity of p65 to I κ B α , facilitating its activation (136). Similar regulatory patterns have been observed in other types of malignancy, including pancreatic, cervical and colorectal cancer (49,137,138). Further, O-GlcNAcylation also affects upstream kinases in the NF- κ B pathway. For example, modification of the adaptor protein TAK1-binding protein 1 is essential for transforming growth factor (TGF)- β -activated kinase 1 (TAK1) activation, a key step in NF- κ B signaling (139). Moreover, O-GlcNAcylation of IKK β enhances TNF- α -induced NF- κ B activation, sustaining cell viability in prostate cancer (140).

JAK/STAT signaling. The JAK/STAT pathway governs cytokine-driven inflammation and immunity (135). Ligand binding to cell surface cytokine receptors activates JAK kinases, which phosphorylate STAT transcription factors (135). Phosphorylated STATs dimerize and translocate to the nucleus to drive gene expression (135).

Studies demonstrate that O-GlcNAcylation modulates STAT activity in a context-dependent manner (141,142). In colonic macrophages, O-GlcNAcylation of STAT3 at Thr717 negatively regulates its phosphorylation, paradoxically enhancing inflammation and promoting tumorigenesis (141). By contrast, O-GlcNAcylation of STAT5A facilitates its tyrosine phosphorylation and transcriptional activation, driving myeloid transformation (142).

AP-1/JNK signaling. AP-1 transcription factor family, comprising Jun (c-Jun, JunB, JunD) and Fos (c-Fos, FosB, Fra1, Fra2) proteins, is activated via the JNK pathway and serves a critical role in inflammation and oncogenesis (135). In HCC associated with non-alcoholic fatty liver disease, OGT promotes tumor progression by enhancing JNK/c-Jun/AP-1 signaling (35). Further, evidence from non-small cell lung cancer indicates that mannose suppresses tumor growth and inflammation by downregulating Jun mRNA stability. Mechanistically, this occurs via inhibition of heterogeneous nuclear ribonucleoprotein R O-GlcNAcylation, decreasing Jun mRNA stability and subsequent IL-8 transcription (143).

Hh signaling. Hh signaling regulates differentiation and function of key immune cells through O-GlcNAc-mediated reprogramming of intracellular metabolic networks. In breast cancer, active Hh signaling shifts macrophages toward the M2 phenotype, a process that depends on HBP flux and O-GlcNAcylation of STAT6 (144). Inhibition of Hh reprograms these macrophages toward a pro-inflammatory M1 phenotype (144). Moreover, Hh signaling governs regulatory T (Treg)/T helper (Th) cell 17 balance through O-GlcNAcylation of lineage-defining transcription factors FOXP3 and STAT3 (145). Suppressing Hh signaling facilitates the transdifferentiation of Tregs into Th17 cells, enhancing CD8⁺ T cell infiltration and anti-tumor immunity (145).

Reciprocally, O-GlcNAcylation promotes Hh pathway activity via direct modification of GLI1 and GLI2, the primary transcription factors of Hh signaling, enhancing

their transcriptional output (146,147). In breast cancer, this axis drives the expression of drug resistance genes such as ATP binding cassette subfamily B member 1 (ABCB1), ABC subfamily G member 2, ERCC excision repair 1 endonuclease non-catalytic subunit and X-ray repair cross complementing 1, which are Hh pathway target genes (146).

O-GlcNAcylation in immune cell function. Beyond direct cell effects, chronic inflammation shapes the TME, creating a fertile ground for CCA progression. Tumor-associated macrophages (TAMs), often polarized to an M2-like phenotype, contribute to the pro-tumorigenic milieu by secreting growth-promoting factors (134). The chronic inflammatory microenvironment not only initiates and promotes cholangiocarcinogenesis but also contributes to the aggressive nature and inherent chemoresistance of CCA, posing challenges for therapeutic intervention. Accumulated reports suggest that O-GlcNAcylation affects the TME (140,148-156), shaping immune responses and stromal remodeling that collectively support CCA progression.

Macrophages. TAMs are key constituents of the TME and are broadly categorized into pro-inflammatory M1 and immunosuppressive M2 phenotypes (135). O-GlcNAcylation promotes M2 polarization in various types of cancer, including colorectal and pancreatic malignancies (148,149), favoring tumor immune escape. In pancreatic cancer, GFPT2, the key enzyme in HBP pathway, drives HBP flux and enhances M2 polarization via O-GlcNAcylation of Y-box binding protein 1, promoting IL-18 expression and tumor progression (149). Moreover, O-GlcNAcylation of the protease cathepsin B facilitates its maturation and secretion, further supporting tumor metastasis (150). Hyperglycemia, which elevates systemic O-GlcNAcylation levels, also promotes M2 polarization in colorectal (148) and breast cancer (151). In diabetic mice, normalization of blood glucose decreases M2 infiltration and metastasis (151). Under inflammatory conditions such as lipopolysaccharide (LPS) stimulation, reduced O-GlcNAcylation has been observed, and modification of RIPK3 attenuates pro-inflammatory signaling, highlighting a dual role of O-GlcNAcylation depending on context (130).

Lymphocytes. Lymphocyte subsets, including CD8⁺ cytotoxic T, CD4⁺ Th (Th1, Th2, Th17, Tregs), B and natural killer (NK) cells, are integral to tumor immunosurveillance (135). O-GlcNAcylation is essential for T cell differentiation, particularly affecting progenitors (152), effector/memory CD8⁺ T (153,154) and Th17 cells (155) and Tregs (156). Hinshaw *et al* (145) demonstrated that Hh-driven O-GlcNAcylation promotes the transdifferentiation of Tregs to Th17 cells via modification of FOXP3 and STAT3, promoting tumor immune eradication by CD8⁺ T cells (145). Moreover, tumor-derived exosomes enriched in OGT upregulate PD-1 expression in CD8⁺ T cells, enabling immune evasion esophageal carcinoma (157). Further, O-GlcNAcylation in NK cells suppresses cytotoxic function and fosters immunotolerance (158,159).

Fibroblasts. Cancer-associated fibroblasts (CAFs) mediate extracellular matrix remodeling and contribute to the desmoplastic stroma characteristic of CCA, supporting

Table III. Commonly used cell-permeable O-GlcNAc transferase inhibitors.

A, UDP-GlcNAc analogs					
Compound	IC ₅₀ , μM	Key characteristics	Number of papers in PubMed ^a	Available <i>in vivo</i> data in mammal	(Refs.)
Alloxan	~100	Uracil analog, high off-target effects and toxicity, also inhibits OGA	>8,000	Yes	(161)
5SGlcNH ₆	N/A	Metabolically converted to UDP-5SGlcNH ₆ in cells	2	Yes	(162)
BADGP	N/A	Lacks specificity	6	Yes	(163)
B, Small molecule inhibitors from high-throughput screening					
Compound	IC ₅₀ , μM	Key characteristics	Number of papers in PubMed ^a	Available <i>in vivo</i> data in mammal	(Refs.)
ST045849	53±7	Potential off-target effects and toxicity	9	Yes	(164)
L01	21.8	Natural compound	2	No	(165)
OSMI-1	2.7	Does not affect N- or O-linked polysaccharides on cell surface	50	Yes	(166)
OSMI-4	3	Best reported cell activity among OSMI compounds	6	No	(167)

^aAs of 9 June 2025, excluding review papers. UDP-GlcNAc, uridine diphosphate N-acetylglucosamine; OGA, O-GlcNAcase; 5SGlcNH₆, 2-deoxy-2-N-hexanamide-5-thio-d-glucopyranoside; BADGP, benzyl-2-acetamido-2-deoxy-α-D-galactopyranoside; N/A, not available.

tumor proliferation, invasion and therapeutic resistance (132,134,135). In fibroblasts, O-GlcNAcylation of IKKβ enhances TNF-α-mediated NF-κB signaling, reinforcing pro-tumorigenic pathways (140).

In conclusion, O-GlcNAcylation is potentially a key regulatory node at the intersection of inflammation, immunity and tumor progression in CCA. Through its modulation of key transcription factors, immune cell function and stromal remodeling, O-GlcNAcylation sustains an environment conducive to malignancy. Its dual role in promoting tumor-associated inflammation while decreasing anti-tumor immunity positions it as a promising target for therapeutic intervention. Further elucidation of cell-specific and context-dependent effects is key for developing precision immunotherapy and metabolic targeting strategies in CCA.

O-GlcNAcylation affects cancer drug response. Given the key role of O-GlcNAcylation in a range of pathological conditions, including cancer, considerable efforts have been directed toward the development of OGT inhibitors (OGTis) (160-167). These inhibitors generally fall into two categories: Substrate analogs and small molecules identified through high-throughput screening (160). Despite progress, the usage of OGTis remains limited, primarily due to challenges associated with specificity and cell permeability (160). The current landscape of OGT inhibition strategies has been comprehensively reviewed (160). Commonly utilized OGTs in preclinical research and their advantages and limitations

are summarized in Table III. Certain classes of OGTis, such as non-cell-permeable compounds (goblin 1 and 2) and irreversible inhibitors, [such as uridine 5'-diphospho-2-deoxy-2-(2*E*)-1-oxo-4-chloro-2-buten-1-yl]amino]-5-thio-α-D glucose and benzoxazolinone (BZX)], have limited applicability in cellular systems (160). Among the OGTis developed to date, the OSMI series, particularly OSMI-1 and OSMI-4, developed by Harvard Medical School, Boston, USA are the most widely used and well-characterized. Compared to other compounds in the OSMI series, OSMI-4 exhibits higher potency and improved pharmacological properties, however, OSMI-1 remains the most commonly utilized due to its earlier availability and documented efficacy in both *in vitro* and *in vivo* models.

O-GlcNAcylation has emerged as a notable factor influencing cancer treatment responses. Recent studies indicate that O-GlcNAcylation plays a crucial role in mediating resistance to radiation and chemotherapies (168,169). In MCF7 breast cancer cells, increased O-GlcNAcylation protects tumor xenografts against radiation (168). Conversely, decreasing O-GlcNAcylation through OGT inhibition results in suppressed cancer proliferation and delayed DNA double-stranded break (DSB) repair, and promotes senescence *in vivo* (168). Similar effects have been observed in the murine pancreatic ductal adenocarcinoma cell line Panc02 (168). These findings underscore the key role of OGT and O-GlcNAcylation in the repair of radiation-induced DNA DSBs. However, further investigation is needed to determine whether combining OGT inhibition

Table IV. Drug classes and anticancer therapies with benefits when combined with O-GlcNAc transferase inhibition.

Treatment	Type of cancer	(Refs.)
Doxorubicin	Liver	(55)
Docetaxel	Lung	(63)
Dabrafenib	Melanoma	(63)
GPT2 inhibitor	Prostate	(70)
Tumor necrosis factor-related apoptosis-inducing ligand	Colon	(112)
SN-38 (active metabolite of irinotecan), etoposide	Colon (with active p53)	(114)
Radiation-induced DNA double-stranded break	Breast, pancreatic	(168)
PD-L1 inhibitor	Liver	(173,174)
Proteasome inhibitor	Breast, lung, osteosarcoma, melanoma	(181,182)
Docetaxel	Prostate	(184)
Methotrexate	Osteosarcoma	(185)
PI3K inhibitor	Breast, ovarian	(186)
Regorafenib	Colon	(187)
CDK7 inhibitor	Castration-resistant prostate	(188)
CDK9 inhibitor	Prostate	(189)
CDK9 inhibitor	Liver	(190)

GPT, glutamic--pyruvic transaminase 2; SN-38, 7-ethyl-10-hydroxycamptothecin.

with DNA DSB-inducing therapy, such as topoisomerase inhibitors or platinum-based DNA crosslinkers, yields similar benefits to radiation-induced DNA DSBs. Ping and Stark (170) indicated that OGT is essential for homology-directed repair but not non-homologous end joining. Furthermore, a previous study demonstrated a positive reciprocal regulatory association between OGT and the cell DNA damage response pathway, which sustains cell proliferation (171). High glucose levels are associated with increased O-GlcNAcylation, resistance to 5-fluorouracil (5-FU) and radiation in rectal cancer (169).

Immune checkpoint inhibitors are a novel class of cancer treatments that have shown potential benefits across a range of malignancies (172). However, O-GlcNAcylation contributes to resistance against these therapies (173). For example, in liver cancer cell lines, OGT-mediated O-GlcNAcylation prevents the degradation of programmed death-ligand 1 (PD-L1), thereby promoting immune escape of cancer cells (173). Notably, combining O-GlcNAc inhibition with PD-L1 monoclonal antibodies has been shown to enhance tumor immune eradication *in vivo* (173,174).

Proteasome serves a key role in maintaining cellular homeostasis by regulating protein turnover, recycling amino acids and clearing misfolded or damaged proteins, particularly under stress conditions to prevent toxic aggregation. In cancer, increased proteasome activity supports tumor progression by promoting the degradation of misfolded and tumor suppressor proteins and maintaining high translational demand (175-177). This dependency underpins the clinical use of proteasome inhibitors such as bortezomib, carfilzomib and ixazomib in cancers (178,179). However, their therapeutic efficacy is limited by adverse effects and acquired resistance (178,179).

O-GlcNAcylation has emerged as a critical modulator of proteasome function (180-182). Traditionally considered an inhibitor of proteasomal activity, O-GlcNAcylation of the

19S regulatory subunit suppresses proteasome function (180). Increased global O-GlcNAcylation is associated with reduced proteasome activity and enhanced apoptosis in both neuronal and cancer cells (180). Paradoxically, under proteasome inhibition, O-GlcNAcylation serves a compensatory, pro-survival role, supporting cell adaptation through multiple mechanisms, such as facilitating NRF1-mediated transcription of proteasome subunits (181), promoting proteasome turnover (182) and enhancing protein translation to generate functional proteins (183). Accordingly, disruption of O-GlcNAc cycling works with proteasome inhibitors to potentiate cancer cell death, offering a potential strategy to overcome drug resistance (181,182).

The interaction between O-GlcNAcylation and cancer therapeutic resistance underscores the potential for developing combination strategies that incorporate OGTis to enhance the efficacy of other anticancer agents (Table IV). Notably, several drugs that benefit from concomitant OGT disruption, such as 5-FU, irinotecan, dabrafenib and immune checkpoint inhibitors, are recommended in standard guidelines for CCA therapy including NCCN 2023 and ESMO 2022 (24,25), further highlighting the potential of OGT targeting as a therapeutic strategy for CCA.

3. Conclusion

Given the unsatisfactory treatment response and limited therapeutic options for CCA (20,27-29), targeting OGT as a novel treatment strategy offers a promising avenue for addressing this aggressive malignancy. OGT and O-GlcNAcylation have emerged as key regulators of a multitude of cancer hallmarks, including cancer progression, metastasis, metabolic reprogramming, angiogenesis, programmed cell death, cancer-associated inflammation (Figs. 4 and 5) and drug response. *In vitro* and

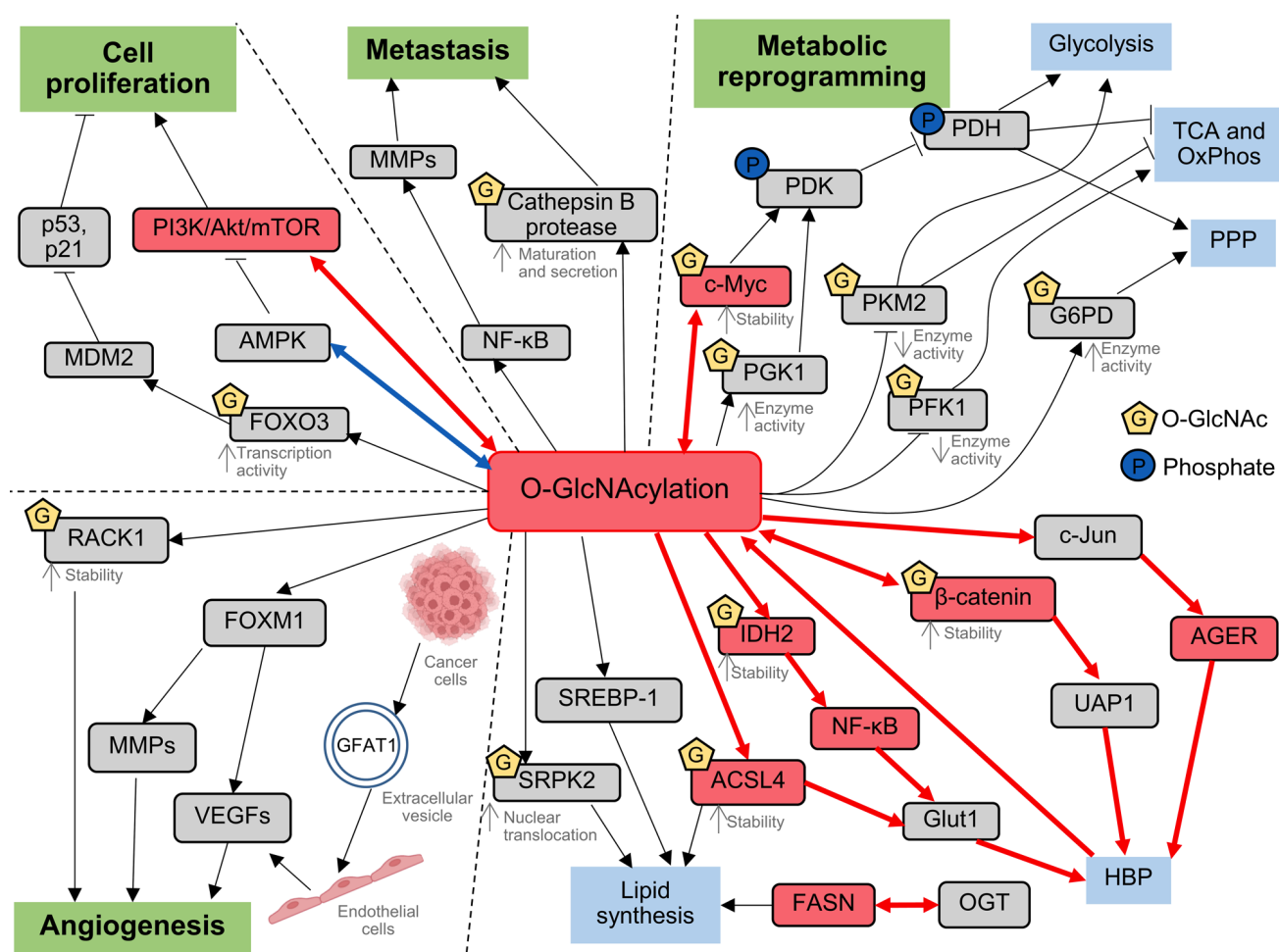


Figure 4. Schematic representation of the role of O-GlcNAcylation in CCA-relevant oncogenic pathways, including cell proliferation, metastasis, metabolic reprogramming and angiogenesis. Oncogenic regulators that exhibit a positive feed-forward relationship with OGT and/or O-GlcNAcylation, contributing to CCA progression and survival, are highlighted in red. Figure constructed using BioRender (biorender.com/). CCA, cholangiocarcinoma; OGT, O-GlcNAc transferase; MDM2, mouse double minute 2 homolog; PDK, pyruvate dehydrogenase kinase; PDH, pyruvate dehydrogenase; OxPhos, oxidative phosphorylation; TCA, tricarboxylic acid cycle; PKG, phosphoglycerate kinase; PPP, pentose phosphate pathway; PKM2, pyruvate kinase M2; G6PD, glucose-6-phosphate dehydrogenase; PFK, phosphofructokinase; AGER, advanced glycosylation end product-specific receptor; UAP1, UDP-N-acetylglucosamine pyrophosphorylase 1; HBP, hexosamine biosynthesis pathway; IDH, isocitrate dehydrogenase; Glut, glucose transporter; FASN, fatty acid synthase; SREBP-1, sterol regulatory element-binding protein 1; ACSL4, acyl-CoA ligase 4; SRPK2, serine/arginine-rich protein kinase 2; GFAT, glutamine fructose-6-phosphate amidotransferase; RACK1, ribosomal receptor for activated C-kinase 1.

in vivo evidence indicates that reducing O-GlcNAcylation levels in cancer cells induces favorable anticancer responses, such as growth inhibition (31,35,47,49-55) and decreased invasiveness (35,67-69). Furthermore, cancer cells typically exhibit elevated total O-GlcNAcylation and OGT protein expression compared with normal tissues (30-38), suggesting the existence of a therapeutic window that may be exploited. Notably, cancer cells exhibit dependence on elevated O-GlcNAcylation, as this modification supports processes essential for their proliferation and survival. Targeting this pathway may provide therapeutic benefits in CCA.

Our previous study explored the relationship between O-GlcNAcylation-related profiles, including the protein expression of OGT and OGA and total O-GlcNAcylation levels, and the effectiveness of the OGT inhibitor OSMI-1 across eight colorectal cancer cell lines (187). The aforementioned study revealed a stronger correlation between the sensitivity to OGT inhibition and total protein O-GlcNAcylation levels compared with OGT protein expression level (187). Therefore,

total O-GlcNAcylation levels may serve as a better predictive marker for sensitivity to OGT than OGT protein expression. Therefore, cancer exhibiting elevated O-GlcNAcylation levels may be treated via O-GlcNAcylation disruption. A rapid, efficient, and cost-effective method for quantifying O-GlcNAcylation levels in patient samples, coupled with assessment of sensitivity to OGT inhibition, may accelerate the clinical translation of OGT-targeted anticancer therapy. Moreover, since increased glucose availability is known to promote O-GlcNAcylation (68), patients with cancer with comorbidities associated with elevated blood glucose, such as diabetes, may benefit from targeting OGT. Concomitantly, diabetes and obesity are well-established risk factors for CCA (20,23).

OGT and O-GlcNAcylation demonstrate a positive feed-forward relationship with a subset of key oncogenic regulators, collectively driving cancer cell proliferation, survival, metastasis and progression (Figs. 4 and 5). This functional co-dependency may represent an acquired vulnerability (191)

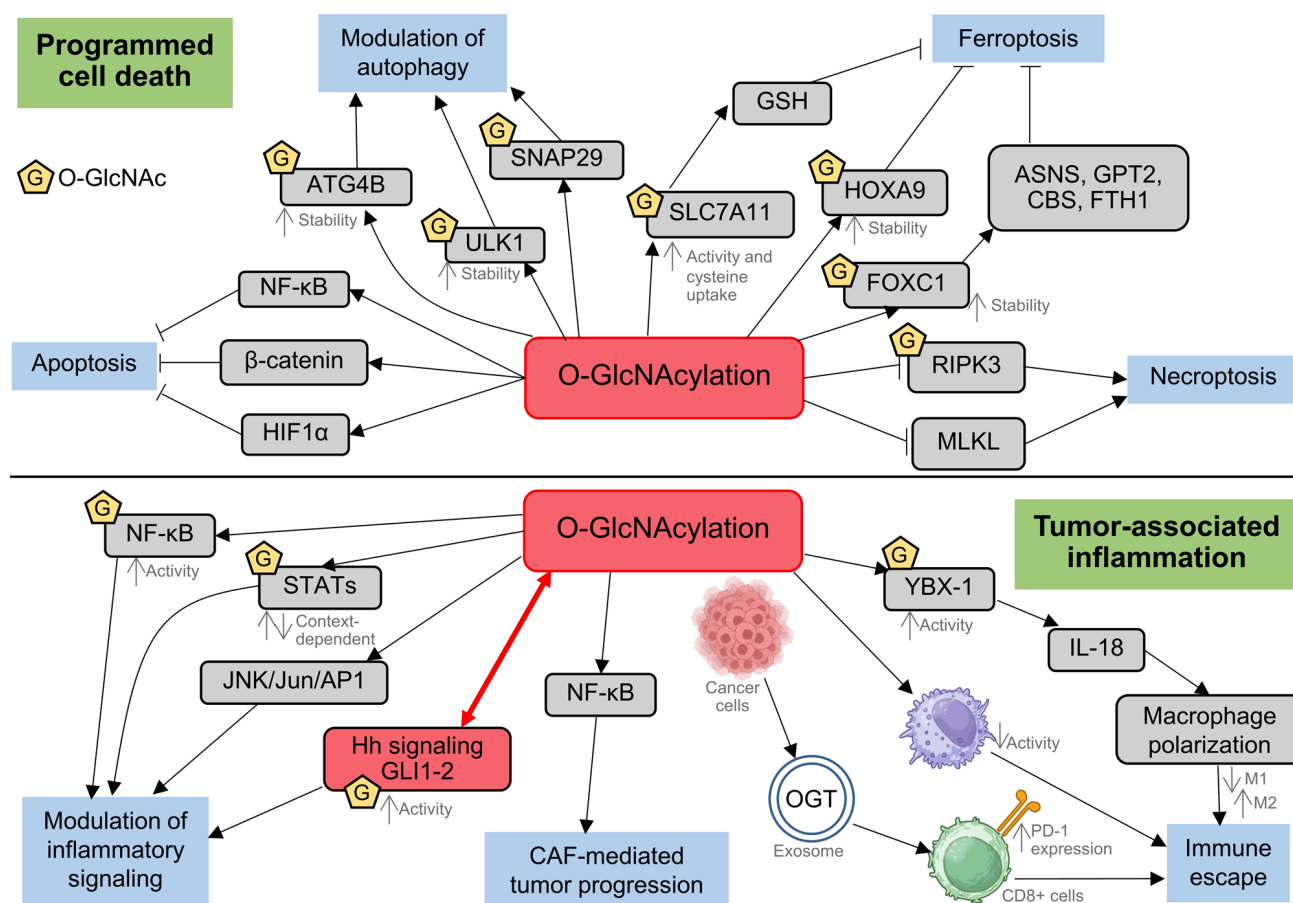


Figure 5. Schematic of the role of O-GlcNAcylation in cholangiocarcinoma-relevant programmed cell death and tumor-associated inflammation pathways. Hh signaling which exhibits a positive feed-forward association with OGT and/or O-GlcNAcylation is shown in red. Figure constructed using BioRender (biorender.com/). Hh, hedgehog; OGT, O-GlcNAc transferase; ATG, autophagy-related protein; ULK1, Unc-51-like kinase 1; SNAP-29, synaptosome associated protein 29; SLC7A11, solute carrier family 7 member 11; GSH, glutathione; ASNS, asparagine synthetase; GPT2, glutamate pyruvate transaminase 2; CBS, cystathionine β -synthase; FTH1, ferritin heavy chain 1; RIPK, receptor-interacting protein kinase; MLKL, mixed lineage kinase domain like pseudokinase; YBX-1, Y-box binding protein 1; CAF, cancer-associated fibroblast; GLI, glioma-associated oncogene homolog.

in CCA, which can be exploited at specific stages to inhibit cancer progression. Targeting OGT alongside these interacting partners may amplify therapeutic effects, particularly in cancers characterized by heightened reliance on these processes. Understanding these dynamics is crucial for developing tailored therapeutic strategies that leverage the vulnerabilities associated with altered O-GlcNAcylation in cancer.

Beyond their direct reciprocal association with O-GlcNAcylation, both AGER and IDH may participate in CCA carcinogenesis in response to environmental toxicants such as polychlorinated biphenyls (PCBs) (192-194). Dioxin-like PCBs (persistent environmental pollutants) have been implicated in hepatic carcinogenesis (195-197). Exposure to PCB congeners such as PCB118, PCB126, and PCB153 is associated with hepatotoxic outcomes in rats, including inflammation, fibrosis, adenoma formation and the development of CCA (195-197). Treatment with Aroclor 1254, a PCB mixture, exacerbates carbon tetrachloride-induced liver injury, as evidenced by decreased glucose-6-phosphatase activity and elevated serum levels of liver enzymes, including serum glutamic-oxaloacetic transaminase and glutamic-pyruvic transaminase, sorbitol dehydrogenase, and IDH (192). Moreover, PCB29-pQ exposure induces ROS production and

promotes the release of high mobility group box 1 in HeLa cells, which activates AGER, contributing to inflammation and disease progression (193). Additionally, co-treatment with LPS and the PCB Aroclor 1248 significantly worsens hepatotoxicity, marked by increased plasma IDH and alanine transaminase activity, implicating neutrophil-mediated injury (194). As both AGER and IDH are regulated by O-GlcNAcylation, these findings suggest a potential mechanistic link between O-GlcNAc signaling and PCB-induced CCA pathogenesis.

Finally, preclinical safety and pharmacokinetic profiling of OGT inhibitors, especially OSMI-1 and OSMI-4, is needed to facilitate clinical translation. While OSMI-4 exhibits improved potency, OSMI-1 has *in vivo* efficacy and is more commonly used in experimental settings. Comprehensive non-clinical evaluation of their safety profile, stability and biodistribution is key for advancing OGTis toward therapeutic application in CCA.

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Availability of data and materials

Not applicable.

Authors' contributions

PC and SJ conceived the study, constructed figures and edited the manuscript. PC performed the literature review and wrote the manuscript. SJ provided overall supervision. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, the large language model ChatGPT (OpenAI) was used solely to improve the readability and language of the manuscript. Subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript. All contents of this review were conceptualized, analyzed and reviewed by the authors.

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