Emerging roles of O-GlcNAcylation in tumorigenesis, immunosuppression and drug resistance (Review)

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Received February 2, 2026; Accepted June 24, 2026

DOI: 10.3892/ol.2026.15743

Abstract. O-GlcNAcylation is a dynamic post-translational modification that is highly sensitive to cellular nutrient availability. Its cycling is tightly regulated by two enzymes with opposing activities: O-GlcNAc transferase (OGT), which catalyzes the addition of N-acetylglucosamine to serine and threonine residues of target proteins, and O-GlcNAcase (OGA), which removes this modification. Accumulating evidence indicates that elevated OGT expression and increased global O-GlcNAcylation are common features of multiple cancer types and are closely associated with tumor initiation, progression and a poor clinical prognosis. Aberrant O-GlcNAcylation plays a critical role in regulating a range of oncogenic processes, including metabolic reprogramming, cell proliferation, metastasis, epigenetic remodeling, immunosuppression and therapeutic resistance. By modifying key signaling molecules, transcription factors and metabolic enzymes, dysregulated O-GlcNAcylation rewires cellular signaling networks to promote malignant transformation and tumor adaptability. In the present review, the recent advances in molecular mechanisms of O-GlcNAcylation in tumorigenesis and cancer progression are systematically summarized. The emerging evidence supporting the therapeutic potential of targeting O-GlcNAcylation and highlight current challenges and future perspectives associated with the development of OGT- and OGA-based anticancer strategies are further discussed. Collectively, a deeper understanding of O-GlcNAcylation-mediated regulatory networks may facilitate the development of novel targeted therapies for cancer treatment.

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Key words: O-GlcNAcylation, tumor metabolic reprogramming, proliferation, metastasis, epigenetic regulation, immunosuppression, drug resistance

Contents

1. Introduction

Cancer is a genetically driven disease defined by uncontrolled cell proliferation triggered by prolonged exposure to various carcinogens. These agents induce genomic and epigenetic alterations, including gene mutations and epigenetic dysregulation. Consequently, such abnormalities disrupt gene transcription, thereby altering the expression of key proteins and enzymes. Notably, these molecular perturbations promote multiple malignant phenotypes, including metabolic reprogramming, therapeutic resistance, sustained proliferation, metastasis and tumor-associated immunosuppression (1,2). More recently, cancer metabolic reprogramming has emerged as a central hallmark of tumorigenesis and cancer progression. Among the key regulatory nodes, the hexosamine biosynthetic pathway (HBP) has attracted increasing attention. As a metabolic hub, the HBP integrates inputs from carbohydrates, amino acids, lipids and nucleotides to generate uridine diphosphate N-acetylglucosamine (UDP-GlcNAc). This nucleotide sugar serves as the essential substrate for protein O-GlcNAcylation, a post-translational modification linking metabolism to cellular signaling (Fig. 1) (3-5). Multiple studies have consistently demonstrated that cancer cells exhibit significantly increased HBP activity, resulting in markedly higher intracellular levels

of UDP-GlcNAc than in healthy cell counterparts. This upregulation is potentially driven by heightened nutrient uptake, particularly of glucose and glutamine, which are subsequently channeled into the HBP (1,4,5). The HBP is initiated when glucose-6-phosphate is isomerized to fructose-6-phosphate. The subsequent rate-limiting reaction is catalyzed by glutamine: Fructose-6-phosphate aminotransferase (GFAT), producing glucosamine-6-phosphate. An alternative route involves GlcNAc kinase phosphorylating glucosamine to yield the same product (Fig. 1). The pathway then proceeds with glucosamine-phosphate N-acetyltransferase, which acetylates glucosamine-6-phosphate using acetyl-CoA, thereby generating GlcNAc-6-phosphate (Fig. 1). This is followed by an isomerization reaction mediated by phosphoglucomutase 3, which produces GlcNAc-1-phosphate (Fig. 1). The final step is executed by UDP-GlcNAc pyrophosphorylase, which condenses GlcNAc-1-phosphate with UTP to yield the end-product, UDP-GlcNAc (3-7) (Fig. 1). UDP-GlcNAc then serves as the component of the O-GlcNAcylation process, which facilitates the attachment of an UDP-GlcNAc moiety to serine or threonine residues on target proteins located in the cytoplasm and nucleus (Fig. 1) (2).

In human cells, O-GlcNAc transferase (OGT) exists as three distinct isoforms: Nucleocytoplasmic OGT (ncOGT), mitochondrial OGT (mOGT) and short OGT (sOGT), which differ in domain architecture and subcellular localization. The longest isoform, ncOGT, contains an N-terminal region, multiple tetratricopeptide repeat (TPR) motifs, a linker domain and a C-terminal catalytic domain and mediates the majority of O-GlcNAcylation events within the nucleus and cytoplasm. By contrast, mOGT possesses a unique N-terminal mitochondrial targeting sequence, nine TPR motifs and the catalytic domain, thereby enabling its specific function in mitochondria. The shortest isoform, sOGT, comprises only two TPR motifs together with the linker and catalytic domain (8).

As the key hydrolytic enzyme in the O-GlcNAcylation cycle, O-GlcNAcase (OGA) exhibits a unique dual-domain organization. Its N-terminal domain confers hydrolytic activity specific to O-GlcNAc, while its C-terminal region constitutes a divergent histone acetyltransferase (HAT)-like module (residues 707-916). This HAT-like domain is functionally inactive as it does not contain the essential residues required for interaction with its canonical cofactor, acetyl-CoA (8). Two principal isoforms of OGA have been identified. The full-length variant, designated long OGA, is predominantly found within the nuclear and cytoplasmic compartments. By contrast, a truncated form known as short OGA localizes specifically to mitochondria, a targeting facilitated by the absence of its C-terminal HAT-like domain (8).

The present review systematically summarizes the molecular mechanisms by which O-GlcNAc modification regulates tumor initiation and progression. It discusses how OGT and OGA modulate multiple malignant biological phenotypes of tumors, including metabolic reprogramming, proliferation, metastasis, epigenetic regulation, immunosuppression and drug resistance, via modifying signaling molecules, transcription factors and key metabolic enzymes. This work further advances the theoretical framework for O-GlcNAcylation in tumors.

2. O-GlcNAcylation in tumor metabolic reprogramming

The metabolic reprogramming in cancer cells, driven by the necessity to support rapid proliferation and biosynthesis, features upregulated glucose and glutamine uptake, which in turn potentiates the HBP flux and elevates the production of its terminal metabolite, UDP-GlcNAc, and therefore, the upregulation of O-GlcNAcylation levels (9). Also, hyper-O-GlcNAcylation functions as feedback to change the cellular nutrient status in regulating cancer cell metabolic reprogramming (9).

O-GlcNAcylation in glycolysis. The metabolic profile of cancer cells is notably characterized by a preference for aerobic glycolysis, a phenomenon known as the Warburg effect. Specifically, cancer cells rely predominantly on glycolytic pathways for energy production rather than on mitochondrial oxidative phosphorylation, even under normoxic conditions that would otherwise support the latter process (10). This metabolic phenotype is accompanied by upregulation of glycolytic enzymes and glucose transporters, thereby enhancing glucose uptake in cancer cells and contributing to elevated O-GlcNAcylation through increased flux through the HBP. Conversely, increased O-GlcNAcylation feeds back to modulate glycolysis by directly modifying glycolytic enzymes and stabilizing key transcription factors.

The glycolytic enzyme phosphofructokinase-1 (PFK1), which catalyzes a critical commitment step in glycolysis, is subject to allosteric inhibition upon O-GlcNAcylation at Ser529. This modification is hypothesized to sterically hinder the substrate-binding site and impede PFK1 oligomerization, thereby suppressing its activity. The consequent attenuation of glycolytic flux redirects glucose catabolism toward the pentose phosphate pathway, enhancing the production of biosynthetic precursors to support cell proliferation (6). O-GlcNAcylation at the Thr255 residue of phosphoglycerate kinase 1 exerts a range of biological effects: It potentiates the catalytic function of the enzyme and facilitates its distribution to mitochondria, thereby synergistically boosting the glycolytic pathway (1). The glycolytic enzyme pyruvate kinase M2 is likewise subject to regulation by O-GlcNAcylation. Specifically, modification at residues Thr405 and Ser406 promotes its oligomerization and enhances catalytic efficiency, thereby driving increased glycolytic flux to support metabolic reprogramming (6). In the tumor microenvironment, IL-8 induces the overexpression of glucose transporter 3 and GFAT in colorectal and lung cancer. This, in turn, promotes increased glucose flux into the HBP and elevates O-GlcNAcylation levels, thereby contributing to the acquisition of cancer stem cell-like properties (11).

O-GlcNAcylation in amino acid metabolism. The rate of UDP-GlcNAc production is determined by metabolic flux through the HBP, which is further modulated by amino acid availability. As this nucleotide sugar serves as the essential substrate for OGT, its intracellular abundance acts as a key determinant of both global O-GlcNAcylation levels and OGT enzymatic activity. Consequently, amino acid metabolism, particularly glutamine metabolism, a critical contributor to the HBP, is tightly linked to the regulation of O-GlcNAcylation (1).

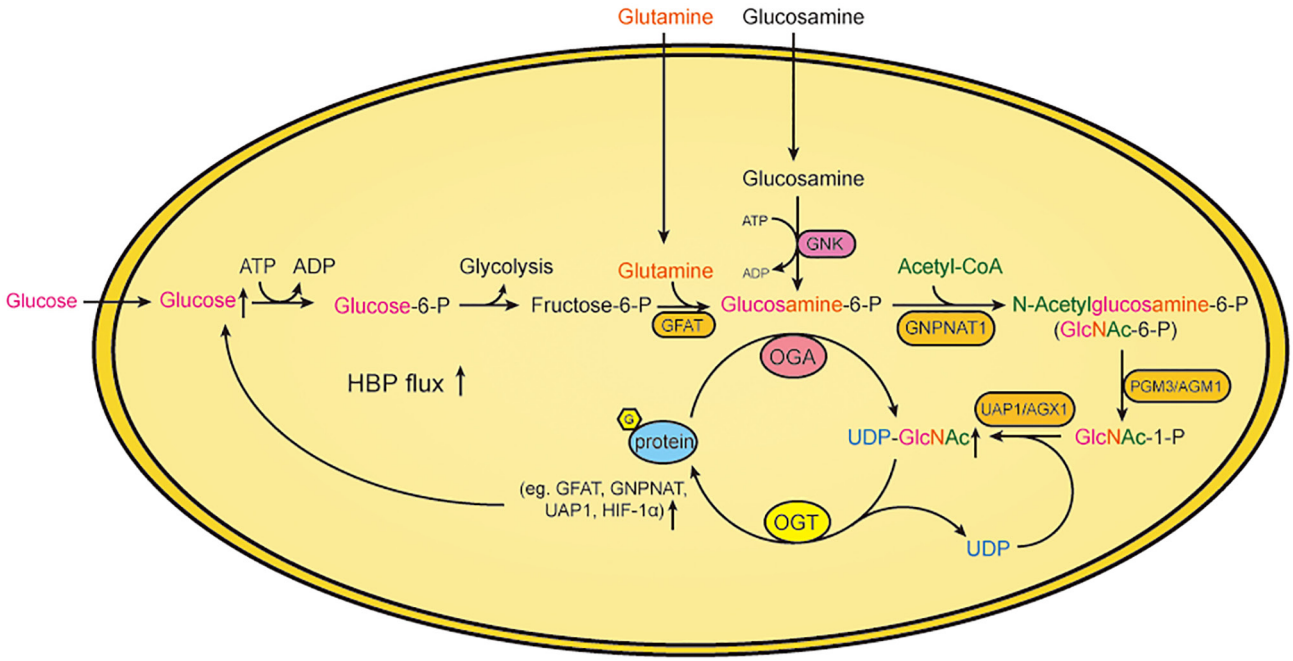

Figure 1. HBP integrates key substrates-including glucose, glutamine and acetyl-CoA- to produce UDP-GlcNAc, a process facilitated by several essential enzymes. HBP initiates the process with the key sugar substrate, glucose-6-phosphate and the amino acid glutamine. GFAT commences the first step that produces glucosamine-6-phosphate. Subsequent acetylation using acetyl-CoA, catalyzed by GNPNAT1, yields GlcNAc-6-P, which is then converted to GlcNAc-1-P through the catalytic activity of the mutase PGM3/AGM1. Finally, UAP1/AGX1 utilizes UTP to produce the terminal product, UDP-GlcNAc. This metabolite serves as an essential building block for O-GlcNAcylation of proteins, linking cellular nutrient status to post-translational modification. In this figure, different groups in UDP-GlcNAc are represented with different colors. Furthermore, O-GlcNAcylation of proteins (e.g., GFAT, GNPNAT, UAP1 and HIF-1α) increases the flux of glucose and HBP, thereby enhancing the level of O-GlcNAcylation. HBP, hexosamine biosynthetic pathway; UDP-GlcNAc, uridine diphosphate N-acetylglucosamine; GFAT, fructose-6-phosphate aminotransferase; GNPNAT1, glucosamine-phosphate N-acetyltransferase 1; GlcNAc-6-P, GlcNAc-6-phosphate; GlcNAc-1-P, GlcNAc-1-phospahte; PGM3. phosphoglucomutase 3; AGM1, N-acetylglucosamine-phosphate mutase 1; UAP1/AGX1, UDP-N-acetylglucosamine pyrophosphorylase 1; UTP, uridine triphosphate; HIF-1α, hypoxia-inducible factor 1α.

The uptake of glutamine is upregulated by oncogenes in cancer cells. For example, the glutamine transporter is transcriptionally upregulated by *c-Myc*. Under hypoxic tumor conditions, hypoxia-inducible factor-1α (HIF-1α) transcriptionally enhances GFAT expression. Conversely, silencing of oncogenic signals, including *Kras* or *c-Myc*, leads to its downregulation in pancreatic cells (9). In summary, HIF-1α and oncogenes increase metabolic flux through the HBP and elevate O-GlcNAcylation levels by upregulating the expression of glutamine transporters and GFAT (9). Conversely, O-GlcNAcylation can regulate amino acid metabolism. Studies demonstrate that pharmacologically inhibiting OGT suppresses the progression of hepatocellular carcinoma and pancreatic tumors, particularly in contexts where the glutamine-synthesizing enzymes remain functional. This finding implies a critical functional dependency on OGT and O-GlcNAcylation for cancer growth, potentially through modulating glutamine metabolism (9,12). Upregulation of OGT and O-GlcNAcylation in colorectal cancer enhances cellular glutamine acquisition through transcriptional activation of the specific transporters solute carrier family 1 member 5 and solute carrier family 38 member 2 (1).

O-GlcNAcylation in lipid metabolism. Since cancer cells prefer aerobic glycolysis, the majority of glucose-6-phosphate is directed into the glycolytic pathway, yielding pyruvate. The pyruvate is subsequently converted into acetyl-CoA, which then enters the mitochondrial citric acid cycle (13). Citrate generated by the citric acid cycle is transported to the cytoplasm, where it is converted into cytosolic acetyl-CoA by ATP-citrate lyase (ACLY). This acetyl-CoA serves as an essential substrate for fatty acid synthesis. Notably, ACLY expression is commonly upregulated in various types of cancer (13). In glioblastoma, phosphatidylinositol 3-kinase (PI3K) phosphorylates OGT at Thr985 and enhances the selectivity of OGT for its substrate, which modifies ACLY at Thr639 and Ser667, promoting acetyl-CoA production to increase fatty acid levels for tumor growth (14,15).

Acetyl-CoA is partly converted into malonyl-CoA through the action of acetyl-CoA carboxylase. Subsequently, both acyl-CoA derivatives undergo condensation to form fatty acids, a reaction catalyzed by fatty acid synthase (FASN) (13). FASN, which catalyzes the final steps of *de novo* fatty acid synthesis, primarily promotes tumor progression by conferring growth and survival advantages to cancer cells rather than merely serving as an anabolic pathway for energy storage (13). It has been demonstrated that OGT plays an essential role in lipogenesis, thereby contributing to tumor progression. OGT promotes sterol response element-binding protein 1 phosphorylation and stability via metabolic control of AMP-activated protein kinase (AMPK) signaling, as well as of the expression of its transcriptional target, FASN (1). Additionally, in the context of liver cancer, FASN has been established as a substrate for O-GlcNAcylation, which subsequently inhibits its ubiquitination and proteasomal degradation, leading to aberrant accumulation of FASN (16). In liver diseases, OGT regulates

hepatic FASN expression and promotes hepatocellular carcinoma progression (17). LIM domain and actin-binding protein 1 (LIMA1) undergoes O-GlcNAcylation catalyzed by OGT at Thr662, which stabilizes LIMA1 by reducing its ubiquitination (17). O-GlcNAcylated LIMA1 regulates FASN expression to enhance lipid accumulation (17).

3. O-GlcNAcylation in cancer cell proliferation

Uncontrolled proliferative capacity, a defining hallmark of cancer cells, is closely associated with a poor clinical prognosis. Accumulating evidence indicates that O-GlcNAcylation plays a critical role in tumor cell proliferation by modulating key biological processes, particularly cell cycle progression and multiple forms of programmed cell death (PCD), including apoptosis and ferroptosis.

O-GlcNAcylation regulates cancer cell cycle progression. The proliferation of malignant tumors depends on continuous mitotic division, a fundamental process required for cellular replication. The cell cycle is broadly divided into two major phases: Interphase, comprising the G1, S and G2 stages, and the mitotic (M) phase. This highly coordinated network is tightly regulated by a series of core regulatory proteins, primarily cyclins and cyclin-dependent kinases (CDKs) (18). Furthermore, key regulatory pathways, including those involving p53, mechanistic target of rapamycin (mTOR) and the forkhead box M1 (FOXM1)-S phase kinase-associated protein 2 (Skp2) axis, play critical roles in governing the cell cycle. Interestingly, OGT has been found to regulate the cell cycle by modifying key factors in these pathways, thereby promoting cancer cell proliferation.

CDK5, a non-canonical member of the CDK family, requires binding to its activator p25 for full enzymatic function. This interaction stabilizes CDK5 by securing its T-loop in an unphosphorylated yet active conformation (19). However, O-GlcNAcylation of CDK5 at Thr246 induces conformational changes in a critical domain of CDK5 and hinders the formation of the CDK5/p25 complex, indicating O-GlcNAcylation at Thr246 promotes the stability of CDK5 (19). Similarly, reduced O-GlcNAcylation of CDK5 induced by melatonin promotes CDK5 degradation (19).

As a master cell cycle regulator, p53 interacts with OGT directly, preventing the degradation of p53 (1). Additionally, OGT modifies other upstream molecules associated with the p53 pathway, such as FOXO3 and VPR-binding protein (VPRBP). O-GlcNAcylation at Ser284 on the FOXO3 protein, which is encoded by a tumor suppressor gene, consists of the tumor-suppressive function of FOXO3 through its interaction with the mouse double minute 2 (MDM2)-p53-p21 regulatory pathway (20). O-GlcNAcylation of FOXO3 at Ser284 activates MDM2, an E3 ubiquitin ligase that primarily regulates p53. This activation leads to the degradation of both p53 and p21, thereby promoting cell cycle progression (20). VPRBP, a shared substrate recognition module that is functionally integrated with both RING-finger cullin4-RING finger Ubiquitin Ligase 4 and the homologous to the E6-AP carboxyl terminus-domain ubiquitin-protein ligase E3 component N-recognin 5 families of E3 ubiquitin ligases, is confirmed to be required in MDM2-mediated p53 ubiquitination (3,21). The O-GlcNAcylation of VPRBP increases its protein stability and activates MDM2, facilitating p53 degradation (21).

The mTOR pathway, upregulated by O-GlcNAcylation, integrates mitogenic cues and nutrient status to promote cell cycle progression (22). In addition, the reciprocal regulatory factor FASN, stabilized by O-GlcNAcylation, activates the mTOR pathway and is also induced by activated mTOR complex 1, which coordinates both cell cycle advancement, particularly the protein synthesis-intensive G1 phase, and overall cellular proliferation (22). Additionally, the anti-autophagic mTOR pathway is inhibited by the upstream regulator AMPK. The activation of AMPK triggers the autophagy process through activating the unc-51 like autophagy activating kinase 1 complex (23). Following this, the class III PI3K complex facilitates autophagosome formation, culminating in the fusion of these vesicles with lysosomes, resulting in the generation of autophagolysosomes (23). O-GlcNAcylation inhibits AMPK phosphorylation, reducing its activity and subsequently suppressing the autophagy process (23).

The FOXM1-Skp2 axis also plays a critical role in cell cycle regulation by modulating the CDK inhibitors p21 and p27. FOXM1 functions as a pivotal transcription factor that drives cellular proliferation by regulating genes essential for cell cycle progression. In several types of cancer, both OGT and FOXM1 expression are concurrently upregulated, leading to transcriptional activation of *Skp2*. As a substrate recognition component of the SCF ubiquitin ligase complex, Skp2 targets p21 and p27 for ubiquitination and proteasomal degradation, thereby facilitating cell cycle progression (24,25). OGT also regulates the stability of FOXM1 indirectly through sirtuin 1 (SIRT1), a NAD+-dependent deacetylase (26). In a previous study, it was found that reducing O-GlcNAcylation activity enhanced AMPK activity, regulating the levels and activity of SIRT1, which can directly deacetylate MEK at lysine 175, thereby suppressing the subsequent activation of ERK, leading to the proteasomal degradation of FOXM (26). Furthermore, O-GlcNAcylation of 6-phosphofructo-2-kinase enables its nuclear import. The ensuing accumulation of Fructose-2,6-bisphosphate in the nucleus subsequently induces Thr187 phosphorylation of the cell cycle inhibitor p27, leading to its degradation and thus facilitating uncontrolled cell division (27). Myc is a transcriptional factor that contributes to cell mitotic division in various types of cancer. In prostate cancer, OGT reinforces the interaction between host cell factor-1 (HCF-1) and Myc, stabilizing key mitotic proteins involved in mitosis, which results in cancer cell proliferation (28).

O-GlcNAcylation regulates PCD. There are several types of PCD that have varying underlying mechanisms, such as apoptosis and ferroptosis (29,30). PCD plays a critical role in maintaining cellular homeostasis and suppressing tumor progression. Emerging research indicates that O-GlcNAcylation is actively involved in modulating PCD, thereby modulating tumor cell proliferation.

The mechanisms of apoptosis primarily involve three pathways: The mitochondrial pathway, the death receptor pathway and the comparatively less characterized endoplasmic reticulum (ER) pathway (31). The ER pathway may be triggered by glucose deprivation in cancer cells, leading to phosphorylation of the PKR-like ER-localized eIF2α kinase and induction of

the C/EBP homologous protein (CHOP) (32). This process upregulates the BH3-only protein Bim of the Bcl-2 family, thereby promoting apoptosis (32). Research indicated that O-GlcNAcylation of HIF-1α enhanced its stability and that of its downstream target glucose transporter, thereby promoting anaerobic glycolysis in cancer cells, ultimately suppressing ER stress and subsequent apoptosis (32). Conversely, OGT can increase cellular palmitate levels by stabilizing FASN, inducing ER stress and initiating oncogenic signaling cascades, including the c-Jun N-terminal kinase/c-Jun/activator protein-1 and NF-κB pathways, thereby promoting cancer cell proliferation (33). Accordingly, O-GlcNAcylation plays a dual role in regulating ER pathway activity. OGT impedes ER stress via increasing anaerobic glycolysis induced by O-GlcNAcylation of HIF-1α, while ER stress is activated by FASN and FASN is stabilized by OGT.

Ferroptosis is an iron-dependent form of regulated cell death characterized by the lethal accumulation of lipid peroxides that disrupt membrane integrity (34). Dysregulated iron metabolism generates excess free iron, which generates reactive oxygen species (ROS), particularly hydroxyl radicals, via the Fenton reaction (35). These ROS trigger lipid peroxidation in membranes, disrupting the integrity of the lipid bilayer and impairing membrane function (35). Emerging research shows that OGT augments HIF-2α stability via deubiquitination, which increases the proportion of polyunsaturated fatty acids in the cell membrane and consequently heightens cellular vulnerability to ferroptosis (36). This finding implies that agents inducing ferroptosis represent a promising therapeutic strategy for cancers characterized by OGT overexpression (36). Conversely, OGT can also inhibit ferroptosis in cancer cells. Eukaryotic translation initiation factor 3 subunit H (EIF3H) interacts with OGT. Reduced *EIF3H* expression has been shown to lower intracellular lipid peroxides and ferrous ion levels, suggesting a synergistic inhibitory role of EIF3H and OGT in ferroptosis within cancer cells (37).

4. O-GlcNAcylation in cancer cell metastasis

The dissemination of cancer cells from the primary tumor to secondary sites, a process directly linked to unfavorable clinical outcomes, is a major driver of cancer progression. These cells can invade peripheral tissues, breach vascular walls, enter the circulation and subsequently travel to distant anatomical sites where they form metastases. Studies indicate that OGT and O-GlcNAcylation facilitate cancer metastasis by modulating the stability and expression of key proteins and genes, as well as by driving the epithelial-mesenchymal transition (EMT) process.

O-GlcNAcylation regulates the stability of proteins and gene expression. Studies have demonstrated a direct functional role for OGT and its catalytic product, O-GlcNAcylation, in controlling the metastatic cascade via influencing the stability of proteins and gene expression.

In breast cancer, suppression of OGT hinders *MORC* family CW-type zinc finger 2 (MORC2)-driven migration and invasion of cancer cells *in vitro*, as well as their ability to colonize lung tissue *in vivo* (38). MORC2 is a novel oncoprotein exhibiting elevated expression across multiple cancer types and leads to the progression of cancers. O-GlcNAcylation of MORC2 at Thr556 enhanced its recruitment to the promoters of connective tissue growth factor (CTGF) and snail family transcriptional repressor 1 (SNAIL), target genes of transforming growth factor β1, and enhanced their transcriptional activity. CTGF and SNAIL are critically involved in breast cancer metastasis (38). Diminished OGT expression results in decreased levels of matrix metalloproteinases (MMPs), such as MMP-2 and MMP-9, and vascular endothelial growth factor, contributing to the inhibition of tumor angiogenesis and metastasis (3,24,26). In papillary thyroid cancer, Yes-associated protein (YAP), a transcription regulator, is a substrate of OGT and undergoes O-GlcNAcylation at Ser109, which inhibits YAP phosphorylation and enhances its transcriptional activity (39). O-GlcNAcylated YAP translocates to and accumulates in the nucleus, where it binds to TEA domain transcription factors. This complex drives the expression of genes that facilitate cancer cell proliferation, invasion and migration (40). B lymphoma Mo-MLV insertion region 1 homolog (Bmi-1) is a transcriptional repressor highly expressed in prostate cancer. OGT mediates O-GlcNAcylation of Bmi-1 at Ser255, thereby increasing its stability. Bmi-1 regulates the *TP53, PTEN* and *CDKN1A*/*CDKN2A* pathways, thereby promoting oncogenic effects (3,41). In colon cancer, X-linked inhibitor of apoptosis protein (XIAP) and OGT mutually regulate cancer cell invasion. XIAP functions as an E3 ubiquitin ligase that is associated with OGT. Conversely, XIAP itself is modified by OGT at Ser406. This modification is essential for XIAP to execute its E3 ubiquitin ligase activity, which directs ubiquitination specifically toward OGT and promotes its proteasomal degradation, thereby inhibiting tumorigenesis (42). A study found that cell migration-inducing hyaluronidase promotes nuclear translocation of β-catenin by increasing its O-GlcNAcylation, thereby elevating both the mRNA and protein levels of c-Myc and promoting cancer cell metastasis through profound rewiring of glutamine metabolism (43).

O-GlcNAcylation regulates EMT. During metastasis, cancer cells undergo a phenotypic shift characterized by the loss of epithelial features and the acquisition of mesenchymal properties. This transition enhances invasive and migratory capacities while conferring increased resistance, collectively promoting metastatic potential. This process, termed EMT, is facilitated by upregulation of OGT and elevated O-GlcNAcylation driven by activation of the HBP and GFAT, thereby promoting cancer cell metastasis (1).

In hepatocellular carcinoma, for example, FOXA2 undergoes O-GlcNAcylation, a modification critical for reducing its transcriptional activity (44). This reduced activity leads to decreased expression of its downstream target, E-cadherin, thereby promoting EMT and enhancing cancer cell migration and invasion. Furthermore, a transcription regulator, CCAATT/enhancer-binding protein β (CEBPB), increases GFAT expression and upregulates O-GlcNAcylation. CEBPB is inhibited when it binds with CHOP (45). Elevated O-GlcNAcylation of CHOP suppresses its ability to form heterodimers with CEBPB and facilitates the DNA-binding activity of CEBPB, enhancing O-GlcNAcylation, which plays a pivotal role in EMT (45).

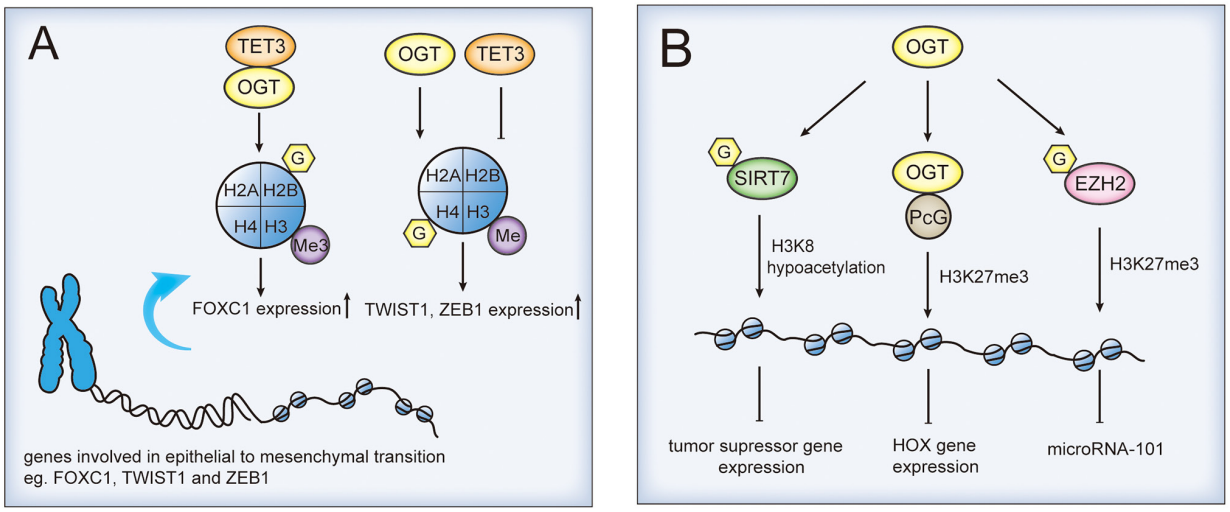

Figure 2. O-GlcNAcylation in epigenetics regulatory mechanisms. (A) Increased TET3 causes enhanced recruitment of OGT and promotes histone H2B O-GlcNAcylation and H3K4 trimethylation modification, which increases FOXC1 expression. O-GlcNAcylation of H4S112 and methylation of H3K4 mediated by OGT result in increased expression of ZEB1 and TWIST1, while TET3 decreases O-GlcNAcylation and methylation. Elevated expression of the FOXC1, TWIST1 and ZEB1 genes promotes the EMT process. (B) OGT modulates gene expression via transcription factors. OGT catalyzes SIRT7 O-GlcNAcylation at Ser136 to stabilize SIRT7, which induces H3K8 hypoacetylation and silences tumor suppressor genes. It also interacts with PcG complexes, strengthens their stability and aids PcG-mediated *HOX* gene repression. Additionally, *miR-101* post-transcriptionally downregulates OGT and EZH2. O-GlcNAcylation stabilizes EZH2; the accumulation of modified EZH2 and H3K27me3 at the *miR-101* promoter represses *miR-101* transcription and further drives EMT. TET3, ten-eleven translocation; OGT, O-GlcNAc transferase; H3K4, histone H3 at lysine 4; FOXC1, forkhead box C1; H4S112, histone H4 at serine 112; ZEB1, zinc finger E-box-binding homeobox 1; TWIST1, Twist-related transcription factor 1; EMT, epithelial-mesenchymal transition; SIRT7, sirtuin 7; PcG, Polycomb group; HOX, homeobox; miR, microRNA; EZH2, enhancer of zeste homolog 2; Me, methylation; Me3, trimethylation.

5. O-GlcNAcylation in epigenetic regulation

Tumorigenesis is driven by cumulative alterations in both the genome and the epigenome. Epigenetics encompasses heritable changes in chromatin structure, including DNA methylation and histone post-translational modifications, which regulate gene expression and thereby play a critical role in cancer pathogenesis (6). Dynamic O-GlcNAcylation is associated with epigenetic changes through various mechanisms, including targeting of chromatin and epigenetic regulators (9,46). This section will explore the function of O-GlcNAcylation within epigenetic regulatory mechanisms.

O-GlcNAcylation participates in chromatin modification. Chromatin is composed of DNA wrapped around histone protein complexes. Each histone octamer consists of two subunits each of H2A, H2B, H3 and H4, which form the nucleosome core that organizes and condenses DNA (47). OGT can target chromatin by mediating DNA methylation and histone post-translational modifications, thereby influencing chromatin structure and gene expression.

The ten-eleven translocation (TET) protein family, comprising TET1, TET2 and TET3, orchestrates active DNA demethylation through a multistep oxidation process. The resulting oxidation products, such as 5-formylcytosine and 5-carboxylcytosine, can subsequently be excised by thymine DNA glycosylase in a TET-dependent manner, thereby promoting DNA demethylation. Dysregulation of this process contributes to genomic instability, a hallmark of tumorigenesis (46,48). It has been shown that TET2 reduces DNA methylation and recruits OGT to transcriptionally active promoters, thereby increasing the transcription of genes involved in cancer cell proliferation (6).

In endometrial cancer cells, TET3 influences the transcription of *FOXC1*, Twist-related transcription factor 1 (*TWIST1*) and zinc finger E-box-binding homeobox 1 (*ZEB1*), key transcription factors involved in EMT, through histone modification. Notably, these factors interact with OGT and participate in EMT regulation (49). Increased TET3 levels increase recruitment of OGT to the FOXC1 genomic locus, coincident with elevated levels of histone H2B O-GlcNAcylation and histone H3 at lysine4 (H3K4) trimethylation, which increases *FOXC1* expression (Fig. 2A) (49). O-GlcNAcylation of histone H4 at Ser112 (H4S112) and methylation of H3K4, both mediated by OGT, enhance the expression of ZEB1 and TWIST1. Conversely, TET3 reduces both O-GlcNAcylation and methylation at these residues (Fig. 2A) (49). SIRT7, a NAD+-dependent deacetylase, facilitates transcriptional silencing of specific tumor suppressor genes by promoting hypoacetylation at histone H3K8. A study indicated that OGT directly interacts with SIRT7, catalyzing its O-GlcNAcylation at Ser136, thereby enhancing SIRT7 stability by impeding its association with the regulator γ of the 11S proteasome complex-mediated proteasomal degradation machinery (50) (Fig. 2B). Polycomb group (PcG) proteins constitute a heterogeneous class of chromatin-associated factors that function as central epigenetic modulators and transcriptional repressors, which can inhibit the expression of homeobox (*HOX*) gene by trimethylating H3K27 (46,51) (Fig. 2B). Importantly, elevated *HOX* gene expression has been closely associated with a wide spectrum of cancers (51). Evidence suggests that OGT participates in repression of *HOX* gene mediated by PcG and interacts with core components of the major PcG repressive complexes (PRC), notably PRC1 and PRC2 (46) (Fig. 2B). Enhancer of zeste homolog 2 (EZH2), which functions as the catalytic subunit of the PRC2 complex, regulates a subset of PRC2

target genes. Notably, through its interaction with OGT, EZH2 influences the expression of these genes, which are commonly perturbed in hormone-signaling-driven malignancies (52). Additionally, OGT and EZH2 expression is coordinately suppressed at the post-transcriptional level by microRNA (miR)-101. O-GlcNAcylation of EZH2 enhances its stability, leading to the accumulation of O-GlcNAcylated EZH2 and a subsequent increase in H3K27 trimethylation at the miR-101 promoter. This epigenetic modification impairs miR-101 transcription, thereby causing the upregulation of OGT and EZH2. Consequently, this positive feedback loop promotes the EMT program and colorectal cancer metastasis (Fig. 2B) (53). HCF-1, a cell cycle regulator, is activated by OGT. By interacting with histone-modifying enzymes such as the H3K9 demethylase lysine-specific demethylase 1 (LSD1), HCF-1 contributes to post-transcriptional histone modifications that drive cell cycle progression in cancer cells (6,51). However, the histone H3K4me1/me2 demethylase LSD2 promotes the proteasomal degradation of OGT through its intrinsic E3 ligase activity, thereby suppressing tumor growth (54).

O-GlcNAcylation participates in epitranscriptomic regulation. Beyond modifications to DNA or histones at the chromatin level, RNA also plays an indispensable role in epigenetic regulation. N6-methyladenosine (m^6A), recognized as one of the most prevalent and functionally critical RNA modification types, is catalyzed by the m^6A methyltransferase complex (55). This complex is composed of three core subunits: Methyltransferase-like 3 (METTL3), METTL14 and Wilms' tumor 1-associating protein, which act synergistically to precisely methylate target RNAs (55). Under physiological conditions in normal hepatocytes, METTL3 protein expression is tightly regulated; the E3 ubiquitin ligase F-box and WD repeat domain-containing 7 (FBXW7) specifically recognizes METTL3 and mediates its ubiquitination (55). Subsequently, ubiquitinated METTL3 is recognized and degraded by the proteasome (55). This dynamic regulatory mechanism not only maintains METTL3 at a relatively stable basal level in hepatocytes, thereby ensuring the homeostatic balance of m^6A modifications on intracellular mRNAs, but also participates in regulating normal physiological metabolism, proliferation and differentiation of cells by moderately inhibiting the stability of target mRNAs (55). By contrast, in hepatoma cells, this finely tuned regulatory network is disrupted. OGT mediates the O-GlcNAcylation of METTL3 at three specific amino acid residues: Thr186, Ser192 and Ser193. This post-translational modification directly interferes with the recognition of METTL3 by FBXW7, thereby blocking the ubiquitination-dependent degradation pathway of METTL3 (55). As a result, METTL3 accumulates abnormally in hepatoma cells, leading to a significant increase in the overall level of m^6A modification in intracellular mRNAs (55). Notably, this elevated m^6A modification enhances the stability of minichromosome maintenance protein 10 (MCM10) mRNA, thereby promoting sustained upregulation of MCM10 expression at both the transcriptional and translational levels (55). Ultimately, the aberrantly increased MCM10 level accelerates the malignant progression of hepatocellular carcinoma by driving uncontrolled cell cycle progression, enhancing cell proliferation and facilitating tumor invasion and metastasis (55).

6. O-GlcNAcylation in immunosuppression

The tumor immune microenvironment (TIME) constitutes a complicated ecosystem consisting of a range of immune cells, including myeloid-derived cells and various lymphocyte populations, alongside extracellular components (56). A suppressive TIME, which is dynamically shaped by continuous crosstalk between the tumor and its infiltrating immune cells, is common in the majority of tumors and promotes tumor immune evasion and is associated with a poor prognosis (57). Recent investigations found that O-GlcNAcylation is instrumental in creating a suppressive TIME. This section synthesizes the crucial influence of O-GlcNAcylation on shaping immune cell phenotypes and promoting immunosuppression in cancer cells.

O-GlcNAcylation in myeloid cells. The composition of myeloid cells in the tumor microenvironment carries significant prognostic value. High densities of dendritic cells typically correlate with improved survival, whereas an abundance of M2-polarized tumor-associated macrophages (TAMs) often serves as a marker of aggressive disease and unfavorable clinical outcomes (58). O-GlcNAcylation influences dendritic cell maturation and inflammatory responses induced by macrophages to promote immunosuppression (59).

TAMs are broadly categorized into two functionally distinct subsets: The pro-inflammatory M1 type, which secretes cytokines, and the anti-inflammatory M2 type, known for releasing distinct signaling factors (57). Elevated O-GlcNAcylation has been shown to drive macrophage polarization toward an M2-like phenotype, thereby facilitating immune evasion and tumor advancement (Fig. 3) (60,61). Conversely, lipopolysaccharide-activated M1-like macrophages demonstrate reduced HBP activity and lower overall O-GlcNAcylation. In this context, the O-GlcNAcylation of receptor-interacting serine/threonine-protein kinase 3 (RIPK3) at Thr467 dampens the receptor-interacting protein homotypic interaction motif-dependent formation of the RIPK3-RIPK1 complex, consequently restraining RIPK3 kinase activation and thereby suppressing inflammation-driven necroptosis in adjacent cancer cells (Fig. 3) (57). Taken together, these findings indicate that O-GlcNAcylation modulates macrophage-mediated inflammatory responses, fostering a TIME conducive to tumorigenesis.

O-GlcNAcylation in lymphocytes. Lymphocytes coordinate anti-tumor immunity through complementary mechanisms. B cells contribute by functioning as antigen-presenting cells and secreting immunomodulatory cytokines, whereas natural killer (NK) cells directly lyse malignant cells through the release of perforin, granzymes and pro-inflammatory cytokines (58). Major T-cell subsets within the TIME include CD8+ cytotoxic T cells and CD4+ helper T (Th) cells. CD4+ T cells, in particular, demonstrate functional diversity upon activation, giving rise to Th1, Th2, Th17 and regulatory T (Treg) cells, which possess distinct functional profiles (57).

Naïve CD8+ T cells undergo differentiation, first developing into effector cells and subsequently into cytotoxic and memory subsets. These activated populations are pivotal for executing anti-tumor immune responses (62). Exosomes, extracellular

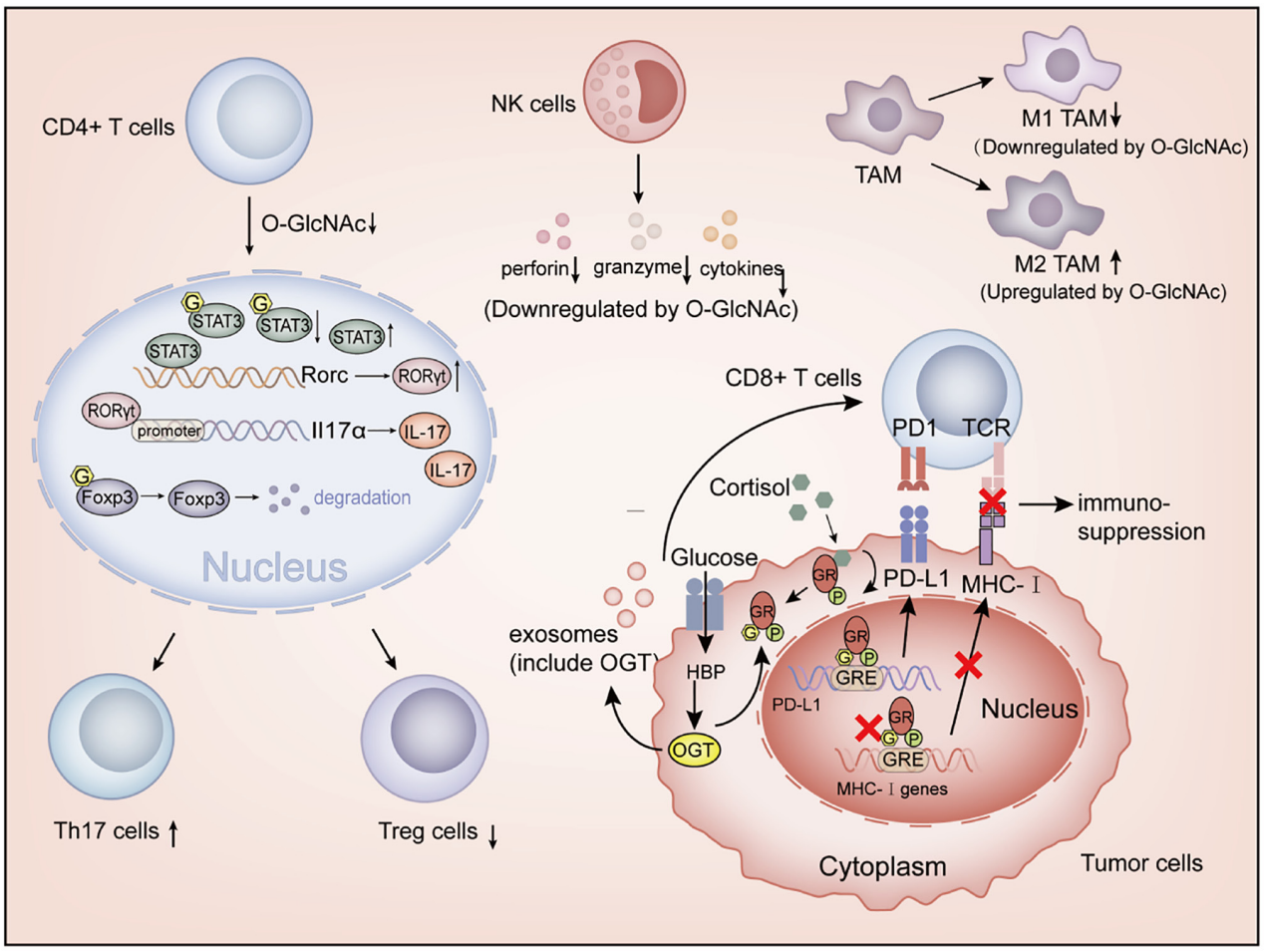

Figure 3. O-GlcNAcylation exerts a profound influence on the TIME by modulating the activity of diverse immune cells. In TAMs, O-GlcNAc drives macrophage polarization toward an M2-like phenotype and the M1-like phenotype is downregulated. In $CD8^+$ T cells, exosomes are internalized by adjacent $CD8^+$ T cells, leading to the upregulation of *PD-1*. O-GlcNAcylated GR enters the nucleus and combines with GRE, inducing *PD-1* expression and reducing *MHC-I* expression. This enhances the *PD-1*/*PD-L1* interaction with tumor cells and promotes immunosuppression. In $CD4^+$ T cells, reduced O-GlcNAcylation decreases FoxP3 stability, thereby weakening Treg-mediated suppression. Conversely, reduced O-GlcNAcylation of STAT3 upregulates the transcription factor RORγt, enhances its binding to the *IL-17* promoter and promotes *IL-17* production, thereby facilitating Th17 differentiation. In NK cells, decreased O-GlcNAcylation impairs cytotoxicity by reducing the secretion of perforin, granzymes and cytokines. TIME, tumor immune microenvironment; TAMs, tumor-associated macrophages; PD-1, programmed cell death protein 1; GR, glucocorticoid receptor; GRE, glucocorticoid receptor element; MHC-I, histocompatibility complex class I; PD-L1, programmed death-ligand 1; FoxP3, forkhead box P3; STAT3, signal transducer and activator of transcription 3; RORγt, receptor-related orphan receptor γt; IL-17, interleukin-17; Th17, T helper 17 cell; NK cells, nature killer cells.

vesicles secreted by numerous cells, enable intercellular crosstalk by systematically transferring bioactive molecules to influence the physiology of target cells (63). A study showed that cancer-derived exosomes create a microenvironment that promotes tumorigenesis (57). OGT exhibits elevated expression in numerous cancers and could interact with the epidermal growth factor receptor, thereby facilitating its secretion into exosomes (64,65). Exosomal OGT derived from esophageal carcinoma stem cells can be internalized by adjacent $CD8^+$ T cells, leading to the upregulation of programmed cell death protein 1 (PD-1). This enhances PD-1/programed cell death ligand 1 interactions with tumor cells, thereby suppressing anti-tumor immunity (65) (Fig. 3). Not only does the OGT in exosomes promote more PD-1 expression, but the combination of OGT and the phosphorylated glucocorticoid receptor (GR) in uterine corpus endometrial cancer also increases PD-1 expression (Fig. 3). O-GlcNAcylation of phosphorylated GR, mediated by OGT, activates GR (Fig. 3) (66). Activated GR enters the nucleus and combines with the GR element, inducing PD-1 expression and reducing histocompatibility complex class I (MHC-I) expression (Fig. 3) (66). Conversely, increased OGT/O-GlcNAcylation via D-mannose supplementation attenuates T-cell exhaustion and augments T-cell anti-tumor function. Following metabolic conversion to fructose-6-phosphate, D-mannose is shunted into the HBP, thereby facilitating the production of UDP-GlcNAc. Concurrently, D-mannose significantly upregulates OGT expression. OGT then interacts with β-catenin, a central mediator of the Wnt signaling pathway. This interaction specifically enhances O-GlcNAcylation of β-catenin at Ser45, thereby abrogating the phosphorylation of this residue by the glycogen synthase kinase 3β-Axin complex. Consequently, β-catenin escapes ubiquitin-proteasomal degradation, leading to a marked extension of its half-life and substantial enhancement of its protein stability. Stabilized β-catenin translocates to the nucleus, where it forms a transcriptional complex with T-cell factor 1 (TCF1) and lymphoid enhancer-binding factor 1. This complex activates the transcription of stemness-associated genes,

Table I. Function of O-GlcNAcylation in mediating therapeutic resistance varies among different cancer types.

Cancer type	Drug therapy	Resistance mechanism	(Refs.)
Ovarian cancer	Cisplatin	SNAP-29/23 hypo-O-GlcNAcylation boosts autophagy and exosomal drug efflux; miR-181d inhibits OGT to disrupt OGT/KEAP1/NRF2 and confer ovarian cancer chemoresistance.	(74,77,81)
Pancreatic cancer	Gemcitabine and paclitaxel	IFIT3 promotes VDAC2 O-GlcNAcylation via OGT binding to block chemosensitive apoptosis in PDAC.	(75)
Acute myeloid leukemia	Doxorubicin and camptothecin	AKT/XBP1-driven HBP flux upregulates O-GlcNAcylation, suppressing caspase-9/3 cleavage and apoptosis.	(76)
Gastric adenocarcinoma, glioblastoma, colon, lung, cervical and endometrial cancers	Trail therapy	O-GlcNAcylation suppresses DR5 trimerization to block TRAIL-mediated apoptosis.	(78)
Breast cancer	Paclitaxel	OGT stabilizes GATAD2B via O-GlcNAcylation to boost breast cancer stemness and paclitaxel resistance through NuRD.	(82)

including *Tcf7*, C-C motif chemokine receptor 7 and Selectin L, while concomitantly repressing exhaustion markers such as PD-1, T-cell immunoglobulin and mucin domain-containing protein 3 and CD39. Collectively, this regulatory cascade promotes T-cell differentiation toward progenitor-exhausted T cells or stem cell-like memory T cells, while constraining the development of terminally exhausted T cells (67,68). In conclusion, OGT exerts dual regulatory effects on the anti-tumor function of T cells. On the one hand, OGT promotes PD-1 and MHC-I expression, thereby contributing to tumor immunosuppression. On the other hand, OGT interacts with β-catenin to enhance its stability. This activates transcription of stemness-associated genes and downregulates exhaustion marker expression, driving T-cell differentiation toward a stem cell-like memory phenotype and ultimately strengthening their anti-tumor activity.

Additionally, O-GlcNAcylation significantly influences $CD4^+$ T-cell differentiation. Specifically, Tregs typically promote tumor progression by releasing inhibitory cytokines that suppress effector cell activity and promote the expansion of other immunosuppressive populations. By contrast, Th17 cells generally exert anti-tumor effects by recruiting effector cells into tumors and producing interferon (IFN)-γ (69). Hedgehog (Hh) signaling, a key developmental regulator, promotes the differentiation and immunosuppressive function of Tregs. Conversely, inhibition of Hh signaling drives Tregs toward a Th17-like phenotype characterized by a pro-inflammatory gene expression profile (Fig. 3) (70). Mechanistically, Hh signaling alters Treg metabolism through the HBP, modulating the O-GlcNAcylation of FoxP3 and STAT3 (Fig. 3) (70). Reduced O-GlcNAcylation decreases FoxP3 stability, thereby weakening Treg-mediated suppression (Fig. 3) (71). Conversely, reduced O-GlcNAcylation of STAT3 upregulates the transcription factor retinoic acid receptor-related orphan receptor γt, enhances its binding to the *IL-17* promoter, and promotes *IL-17* production, thereby facilitating Th17 differentiation (Fig. 3) (57).

In addition, O-GlcNAcylation influences the cytotoxic function of NK cells through multiple mechanisms. Specifically, decreased O-GlcNAcylation impairs NK-cell cytotoxicity against cancer cells by reducing the secretion of perforin, granzymes and cytokines (72), while increased O-GlcNAcylation enhances the cytotoxic function of NK cells by upregulating genes associated with cellular adhesion and mobility (Fig. 3) (73).

7. O-GlcNAcylation in cancer cell drug resistance

The development of drug resistance represents a major challenge in oncology and is mediated by multiple mechanisms. Studies have increasingly implicated OGT and O-GlcNAcylation as key drivers of therapeutic resistance across diverse cancer types. Accordingly, the roles of O-GlcNAcylation in cancer drug resistance are summarized in Table I.

O-GlcNAcylation promotes drug resistance by inducing autophagy and anti-apoptosis in cancer cells. In ovarian cancer, reduced O-GlcNAcylation enhances resistance to cisplatin, a drug that induces autophagy and exerts cytoprotective effects. Mechanistically, decreased OGT expression lowers O-GlcNAcylation of synaptosomal-associated protein 29 (SNAP-29), thereby facilitating its interaction with vesicle-associated membrane protein 8 (VAMP8) and syntaxin-17 to form the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex that mediates autophagosome-lysosome fusion. This process promotes autophagic flux and ultimately contributes to cisplatin resistance (74). In pancreatic cancer, expression of IFN-induced protein with tetratricopeptide repeats 3 (IFIT3), a key mediator of the IFN response with dual roles in antiviral and inflammatory signaling, is associated with poor prognosis in chemotherapy patients (75). Mechanistically, IFIT3 recruits or stabilizes OGT to enhance O-GlcNAcylation of voltage-dependent anion channel 2 (VDAC2). Given that

Table II. Various targets of OGT and key functions.

Mechanism category	Target	Key function	(Refs.)
Metabolic reprogramming	PFK1	Promoting glycolysis inhibition and redirecting flux to pentose phosphate pathway	(6)
	PGK1	Enhancing glycolysis and promoting mitochondrial translocation	(1)
	PKM2	Promoting glycolysis and driving Warburg effect	(6)
	ACLY	Increasing acetyl-CoA and enhancing lipogenesis	(13-15)
	FASN	Catalyzing fatty acid synthesis and supporting tumor growth	(13,16)
	LIMA1	Stabilizing LIMA1 and promoting lipid accumulation	(17)
Proliferation	p53	Inhibiting p53 and promoting cell-cycle progression	(20)
	FOXO3	Impairing FOXO3 tumor suppressor function	(20)
	FOXM1	Stabilizing FOXM1 and accelerating cell cycle	(24,25)
	CDK5	Stabilizing CDK5 and regulating cell cycle	(19)
	MYC	Enhancing MYC activity and driving proliferation	(28)
	PFKFB3	Promoting nuclear import and facilitating cell division	(27)
	HIF-1α	Enhancing the stability of HIF-1α and anaerobic glycolysis, suppressing apoptosis	(32)
Metastasis	YAP	Inhibiting YAP phosphorylation and promoting invasion	(39,40)
	Bmi-1	Increasing the stability of Bmi-1 and promoting the oncogenic effects	(3,41)
	β-catenin	Stabilizing β-catenin, driving EMT and metastasis	(43)
	TWIST1	Stabilizing TWIST1, enhancing EMT	(44)
	ZEB1	Inducing ZEB1 expression, promoting EMT	(44)
	MORC2	Activating MORC2 and driving breast cancer metastasis	(38)
	FOXA2	Repressing FOXA2, promoting migration	(45)
Epigenetic regulation	EZH2	Stabilizing EZH2 and increasing H3K27me3	(52,53)
	SIRT7	Stabilizing SIRT7 and repressing tumor suppressors	(50)
	Histone H2B	Promoting H2B O-GlcNAcylation	(44)
	Histone H4	Inducing H4S112 O-GlcNAcylation	(44)
	TET2/TET3	Recruiting OGT and altering DNA demethylation	(44,47,49)
	METTL3	Accumulating METTL3, increasing m6A modification level of intracellular mRNAs	(55)
Apoptosis	AKT	Enhancing AKT activity and anti-apoptosis	(76)
	DR5	Inhibiting DR5 oligomerization and promoting TRAIL resistance	(78)
	VDAC2	Stabilizing VDAC2; anti-apoptosis	(75)
	XIAP	Enhancing XIAP E3 ligase activity	(42)
Immunosuppression	RIPK3	Inhibiting RIPK3 and suppressing necroptosis	(57)
	PD-1	Upregulating PD-1 and inducing T-cell exhaustion	(65,66)
	GR	Activating GR, reducing MHC-I expression	(66)
	FoxP3	Stabilizing FoxP3, increasing Treg-mediated suppression	(70)
	STAT3	Decreasing Th17 differentiation	(70)
Drug resistance	SNAP-23	Promoting exosomal drug efflux and cisplatin resistance	(77)
	SNAP-29	Enhancing autophagic flux and cisplatin resistance	(74)
	GATAD2B	Stabilizing GATAD2B, enhancing the stemness properties of CSCs and paclitaxel resistance	(82)

SNAP-29/23, synaptosomal-associated protein-29/23; miR, microRNA; OGT, O-GlcNAc transferase; KEAP1, Kelch-like ECH-associated protein 1; NRF2, nuclear factor erythroid 2-related factor 2; IFIT3, IFN-induced protein with tetratricopeptide repeats 3; VDAC2, voltage-dependent anion channel 2; PDAC, pancreatic ductal adenocarcinoma; XBP, X-box binding protein 1; HBP, hexosamine biosynthetic pathway; DR5, death receptor 5; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; GATAD2B, GATA zinc finger domain containing 2B; NuRD, nucleosome remodeling and deacetylase; PFK1, phosphofructokinase-1; PGK1, phosphoglycerate kinase 1; PKM2, pyruvate kinase M2; ACLY, ATP-citrate lyase; FASN, fatty acid synthase; LIMA1, LIM domain and actin-binding protein 1; FOXO3, forkhead box O3; CDK5, cyclin-dependent kinase 5; PFKFB3, fructose-2,6-bisphosphatase; HIF-1α, hypoxia-inducible factor-1α; YAP, Yes-associated protein; Bmi-1, B lymphoma Mo-MLV insertion region 1 homolog; TWIST1, Twist-related transcription factor 1; ZEB1, zinc finger E-box-binding homeobox 1; MORC2, *MORC* family CW-type zinc finger 2; FOXA2, forkhead box A2; EZH2, enhancer of zeste homolog 2; SIRT7, sirtuin 7; TET2/TET3, ten-eleven translocation 2/3; METTL3, methyltransferase-like 3; XIAP, X-linked inhibitor of apoptosis protein; RIPK3, receptor-interacting serine/threonine-protein kinase 3; PD-1, programmed cell death protein 1; GR, glucocorticoid receptor; MHC-I, histocompatibility complex class I; FoxP3, forkhead box P3; STAT3, signal transducer and activator of transcription 3; Th17, T helper type 17 cell; CSC, cancer stem cell.

VDAC2 knockdown elevates mitochondrial membrane potential and ROS production, thereby inducing apoptosis, IFIT3-driven O-GlcNAcylation of VDAC2 attenuates chemotherapy-induced apoptosis, thereby mediating chemoresistance in pancreatic ductal adenocarcinoma (75). Accumulating evidence demonstrates that O-GlcNAcylation mediated by OGT contributes significantly to the development of chemoresistance, a major cause of treatment failure in oncology. Mechanistically, acute exposure to chemotherapeutic agents such as doxorubicin or camptothecin activates the AKT-X-box binding protein 1 signaling axis, thereby increasing HBP flux and, consequently, O-GlcNAcylation levels. Elevated O-GlcNAcylation, in turn, hinders the cleavage and activation of caspase-9 and caspase-3, thereby blocking apoptosis (76). Furthermore, O-GlcNAcylation of the pro-survival transcription factor AKT enhances its phosphorylation, directly amplifying its anti-apoptotic activity. This modification establishes a positive feedback loop that further increases HBP flux, thereby regulating drug resistance in cancer cells (76).

O-GlcNAcylation regulates drug resistance by modulating receptors on the cell membrane. In ovarian cancer, O-GlcNAcylation of SNAP-23 plays a pivotal role in controlling exosome release. This process depends on the precise anchoring and fusion of vesicles to the plasma membrane, a molecular event orchestrated by a SNARE complex composed of SNAP-23, VAMP8 and syntaxin-4 (77). Reduced O-GlcNAcylation of SNAP-23 subsequently facilitates SNARE complex assembly. This, in turn, increases exosome-mediated cisplatin export, thereby depleting intracellular drug concentrations and conferring chemoresistance in cancer cells (77). Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a therapeutic agent that triggers apoptosis by binding to death receptor (DR)4 and DR5. This interaction leads to the formation of the death-inducing signaling complex (DISC), which subsequently activates caspase-8 and caspase-10, thereby activating downstream caspase-3 and culminating in apoptosis (78). In pancreatic cancer, elevated O-GlcNAcylation reduces DR5 oligomerization, a process essential for DISC assembly. DISC formation is required for the recruitment of Fas-associated death domain and procaspase-8, which serves as the critical trigger for caspase-8 activation and subsequent apoptosis (78). O-GlcNAcylation acts as a negative regulatory checkpoint by preventing the initial trimerization of DR5, thereby functionally desensitizing cells to TRAIL-mediated cell death. Consequently, this modification promotes resistance in cancer cells to TRAIL-based therapy (78). However, another study reports an inverse finding. In certain TRAIL-resistant cancer cells, O-GlcNAcylation appears to facilitate DISC formation and DR4 clustering within lipid rafts, thereby promoting TRAIL signaling and ultimately resulting in apoptosis of cancer cells (79). In summary, O-GlcNAcylation exhibits dual and context-dependent regulation of TRAIL-mediated tumor apoptosis. It impairs DR5-dependent DISC assembly, thereby desensitizing pancreatic cancer cells to TRAIL, whereas it enhances DR4 clustering and apoptotic signaling in certain TRAIL-resistant tumor cells. Such contradictory findings imply that the regulatory role of O-GlcNAcylation is cell-state dependent. Further studies are necessary to clarify its precise mechanism and to reconcile discrepancies in current research.

O-GlcNAcylation regulates drug resistance by modulating transcription factors. In myelodysplastic syndromes and acute myeloid leukemia, O-GlcNAcylation enhances TWIST1 stability by impeding its interaction with ubiquitin E3 ligase Cbl proto-oncogene C (80). TWIST1 binds to the promoter of the OGT gene and activates its transcription. This interaction establishes a positive feedback loop, leading to elevated levels of both TWIST1 and OGT in cancer cells, which thereby mediates resistance to decitabine (80). In ovarian cancer, miR-181d negatively modulates the OGT/Kelch-like ECH-associated protein 1 (KEAP1)/nuclear factor erythroid 2-related factor 2 (NRF2) axis by targeting the 3' untranslated region of *OGT* mRNA, thereby reducing OGT expression and enhancing resistance to cisplatin (81). Decreased OGT levels inhibit KEAP1 glycosylation and attenuate the ubiquitin-mediated degradation of NRF2, thereby promoting its intracellular accumulation. Consequently, enhanced NRF2 activity increases cell survival and inhibits PCD, thereby conferring resistance to chemotherapy in ovarian cancer (81). Breast cancer cell proliferation is governed by cancer stem-like cells (CSCs), whose function and activity are modulated by the nucleosome remodeling and deacetylase (NuRD) complex via histone deacetylation (82). GATA zinc finger domain containing 2B (GATAD2B), a core component of the NuRD complex, is closely implicated in breast cancer pathogenesis (82). OGT mediates O-GlcNAcylation of GATAD2B, thereby preventing GATAD2B from itchy E3 ubiquitin protein ligase-mediated proteasomal degradation (82). Of note, ectopic overexpression of GATAD2B not only enhances the stemness properties of breast cancer CSCs but also confers resistance to paclitaxel-induced apoptosis *in vitro* (82).

8. Conclusions and future perspectives

In conclusion, O-GlcNAcylation catalyzed by OGT plays critical roles in multiple aspects of cancer progression, including metabolic reprogramming, proliferation, metastasis, epigenetic regulation, immunosuppression and drug resistance. Aberrant OGT or OGA activity leads to dysregulated O-GlcNAcylation, thereby disrupting the function and stability of oncogenic proteins (Table II). A central mechanism underlying O-GlcNAcylation-driven tumorigenesis involves the direct modification of key components in oncogenic signaling pathways, such as the mTOR and MYC pathways, thereby activating pro-tumorigenic signaling cascades. Beyond regulating protein activity and stability, O-GlcNAcylation also influences gene transcription through both chromatin-level epigenetic regulation and epitranscriptomic mechanisms. For example, OGT-mediated O-GlcNAcylation of METTL3 at Thr186, Ser192 and Ser193 enhances METTL3 stability, leading to increased m^6A modification of *MCM10* mRNA and subsequent changes in gene expression that support malignant progression (55).

Experimental evidence has revealed substantial differences in OGT expression and O-GlcNAcylation levels between normal and malignant tissues. Furthermore, elevated OGT and O-GlcNAcylation in tumor-bearing animals is associated with a poor prognosis, suggesting that OGT and

O-GlcNAcylation may serve as biomarkers for cancer diagnosis. Consequently, the development of inhibitors targeting OGT or modulators of OGA holds broad application potential. Given the differential expression of O-GlcNAcylation in tumor tissues, OGT inhibitors and OGA modulators can be developed to block aberrant glycosylation that drives tumor progression. Furthermore, such agents may be combined with conventional chemotherapeutics, molecularly targeted drugs or immune checkpoint inhibitors, thereby opening novel avenues for combination therapy and optimizing current anti-tumor regimens.

However, clinical translation remains challenging due to poor tissue selectivity, severe off-target toxicity of OGT inhibitors and the general challenge of specifically targeting O-GlcNAc modifications. To address these limitations, tumor-targeted small-molecule drugs could be engineered and tumor-specific modified substrates selected for targeted therapy, thereby preventing disruption of normal O-GlcNAcylation homeostasis in non-malignant cells. Further exploration of the O-GlcNAcylation regulatory network will advance the translational chain from basic mechanistic research to clinical biomarker screening and the development of novel targeted therapies for tumors, thus highlighting a long-term direction for future studies in this field. Furthermore, whether OGT directly modifies RNA in a manner analogous to phosphorylation remains to be determined. Elucidating this unexplored mechanism may represent an important direction for future research.

Acknowledgements

Not applicable.

Funding

This work was supported by grants from the National Natural Science Foundation of China (grant no. 82372977) and Jiangsu Province Excellent Youth Fund (grant no. BK20240127).

Availability of data and materials

Not applicable.

Authors' contributions

YL and YH contributed to writing the original draft, writing, reviewing and editing the manuscript, creating the figures, and acquisition of funding. SD, HD, SL and YZ were responsible for creating the figures, and writing, reviewing, and editing the manuscript. HY was involved in the conceptualization, writing, reviewing and editing of the manuscript, and supervision and project administration. BY contributed to conceptualization, supervision, and project administration of the study, acquisition of funding, and writing, reviewing and editing the manuscript. 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.

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